

**Strategies Towards Asymmetric Conjugate Trifluoromethylation of  
 $\alpha,\beta$ -Unsaturated Ketones and the Asymmetric Conjugate Addition  
of Boronates to  $\beta$ -Trifluoromethyl  $\alpha,\beta$ -Unsaturated Ketones**

by

Matthew Wawrykow

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## Abstract

Currently, there are no reported methods in the literature for the conjugate addition of the trifluoromethyl group to  $\alpha,\beta$ -unsaturated ketones. A bulk of this thesis focused on developing a method to overcome this problem. Strategies included the preparation of binaphthol-modified trifluoromethylboronates, rhodium-catalyzed conjugate addition of trifluoromethyl bearing reagents and the copper-catalyzed conjugate addition of the trifluoromethylborates. When these methods all proved to be unsuccessful, a different approach was taken towards the ultimate goal of obtaining chiral  $\beta$ -CF<sub>3</sub> compounds.

The development of the asymmetric conjugate additions to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketones proved to be an efficient method for obtaining optically active  $\beta$ -CF<sub>3</sub> compounds. Successful protocols for the addition of alkenyl, alkynyl and aryl groups are on the verge of being optimized based on the groundwork in this thesis. Because so few protocols currently exist for the synthesis of chiral  $\beta$ -CF<sub>3</sub> ketones, these methods will provide a valuable toolkit for the synthesis of novel chiral compounds bearing a trifluoromethyl group.

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## List of Abbreviations

Abbreviation	Name
( <i>R</i> )-Br <sub>2</sub> -BINOL	( <i>R</i> )-3,3'-Dibromo-1,1'-binaphthalene-2,2'-diol
( <i>S</i> )-I <sub>2</sub> -BINOL	( <i>S</i> )-3,3'-Diiodo-1,1'-binaphthalene-2,2'-diol
( <i>R</i> )-JOSIPHOS	(2 <i>R</i> )-1-[(1 <i>R</i> )-1-(Dicyclohexylphosphino)ethyl]-2-(diphenylphosphino)ferrocene
( <i>S</i> )-3,5-Xyl-MeO-BIPHEP	( <i>S</i> )-(-)-2,2'-Bis[di(3,5-xylyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl
Ac	Acetyl
AcOH	Acetic Acid
Alpine-Borane <sup>®</sup>	B-Isopinocampheyl-9-borabicyclo[3.3.1]nonane
BINAP	(±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-Binaphthalene-2,2'-diol
<i>t</i> -Bu	<i>t</i> -Butyl
CSA	Camphorsulfonic acid
DIP-Chloride <sup>™</sup>	(-)-B-Chlorodiisopinocampheylborane
DMF	<i>N,N</i> -Dimethylformamide
DuPhos	1,2-Bis[(2 <i>R</i> ,5 <i>R</i> )-2,5-dimethylphospholano]benzene
ee	Enantiomeric excess
er	Enantiomeric ratio
HOMO	Highest occupied molecular orbital
HPLC	High pressure liquid chromatography
<i>i</i> -Pr	isopropyl
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital

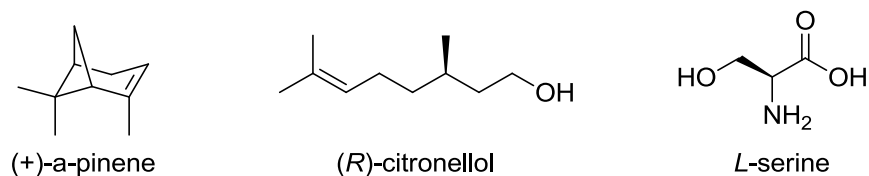
MS	Molecular sieves
NK	Neurokinin
NMR	Nuclear magnetic resonance
<i>o</i> -QM	<i>o</i> -quinone methide
Ph	Phenyl
PhCH <sub>3</sub>	Toluene
rt	Room temperature
TBAF	tetrabutylammonium fluoride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
<i>p</i> -TsOH	<i>p</i> -Toluenesulfonic acid

## Chapter 1: Asymmetric Conjugate Additions

### 1.1 Chirality in Organic Synthesis

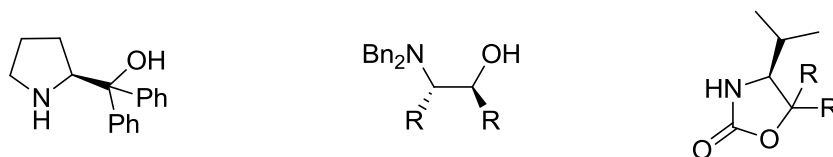
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An integral sector of synthetic chemistry today revolves around the creation of handedness, otherwise known as chirality, in biologically relevant molecules. Traditionally, chirality has been introduced by various means, the most basic taking advantage of a diverse library of starting materials already possessing handedness. This library, commonly referred to as the chiral pool, encompasses various amino acids, monosaccharides and natural products that have been provided as building blocks to chemists by Nature (Figure 1.1).<sup>1</sup>



**Figure 1.1: Common chiral pool reagents**

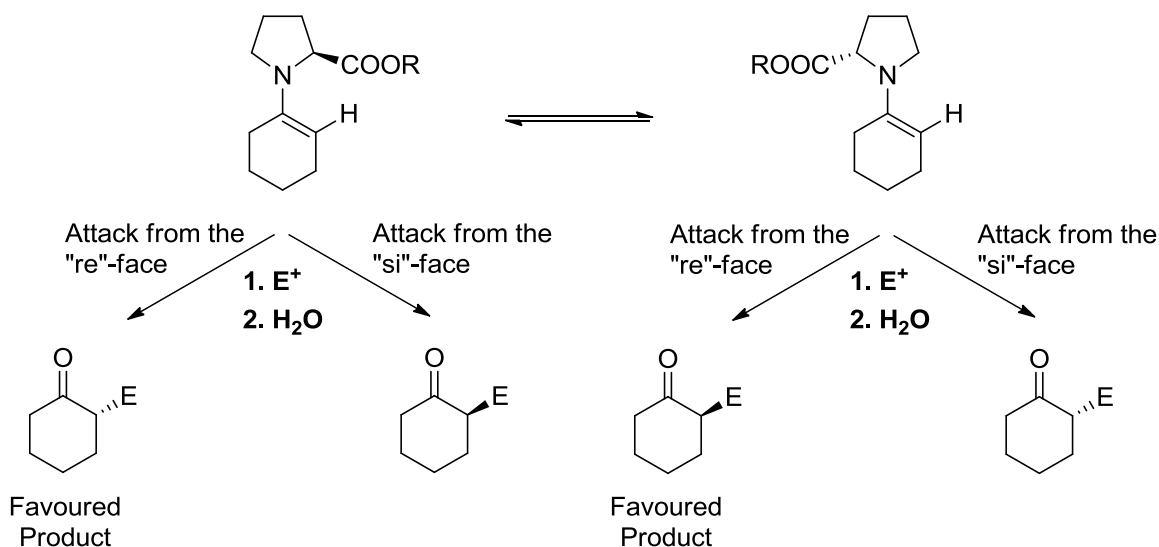
The other classical method of introducing chirality, known as asymmetric induction, makes use of a carefully designed chiral reagent referred to as an auxiliary (Figure 1.2).<sup>2,3</sup> The auxiliary is employed at a specific point in the synthesis to introduce a specific handedness into a compound lacking any three-dimensional configuration (achiral compound). Auxiliaries are often modified derivatives of chiral pool compounds that introduce stereochemistry via steric interactions, but could also involve a favourable interaction such as hydrogen bonding.<sup>2,3</sup>



**Figure 1.2: Commonly used chiral auxiliaries**

An important class of auxiliaries possess  $C_2$  symmetry.  $C_2$  symmetric compounds have an axis of rotation where a  $180^\circ$  turn results in the same geometry as the starting material. Auxiliaries with  $C_2$  symmetry are advantageous in achieving asymmetric induction for various chemical transformations. For example, a  $C_2$  symmetric auxiliary can reduce the number of competing diastereomeric transition states. Of the remaining possible transition states, one is expected to be more favoured than others due to additional steric or electronic interactions.<sup>4</sup>

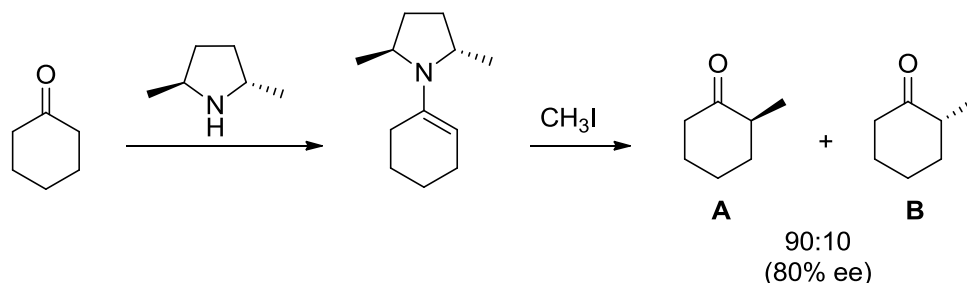
The fortitude of  $C_2$  symmetry in organic synthesis was demonstrated in early attempts at asymmetric alkylations of enamines by Yamada (Scheme 1.1).<sup>5-7</sup> The proline esters employed by Yamada resulted in addition products in low enantiomeric excess (10-30% ee), due to the small difference in energy between the competing transition states.<sup>5-7</sup>



**Scheme 1.1: Poorly selective additions with a non- $C_2$  symmetric auxiliary**

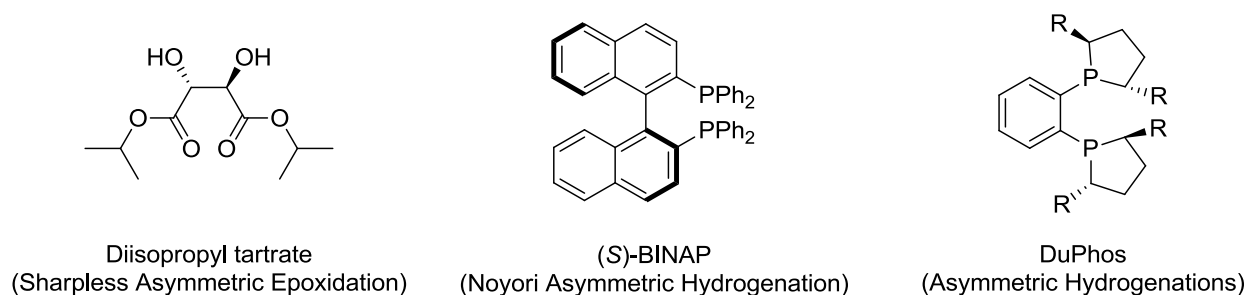
Conversely, Whitesell employed a  $C_2$  symmetrical 2,5-dimethylpyrrolidine for similar alkylations, achieving a much higher enantioselectivity (80% ee).<sup>4</sup> Addition product A is favoured because the addition takes place from the face opposite the methyl-substituent of the

ligand. There is no difference if the enamine is drawn as shown or if the pyrrolidine moiety is rotated 180°. Consequently, attack from the " $\alpha$ -si"-face yields the major product (Scheme 1.2).



**Scheme 1.2: Selective additions with a C<sub>2</sub>-symmetric auxiliary**

Over the years, chemists have found utility in a number of C<sub>2</sub>-symmetric ligands as catalysts or chiral auxiliaries for a wide variety of chemical transformations because of their ability to provide asymmetric products in high enantioselectivities. Some classical C<sub>2</sub>-symmetric ligands and their most recognizable application in synthesis are shown below in Figure 1.3.<sup>8-15</sup>

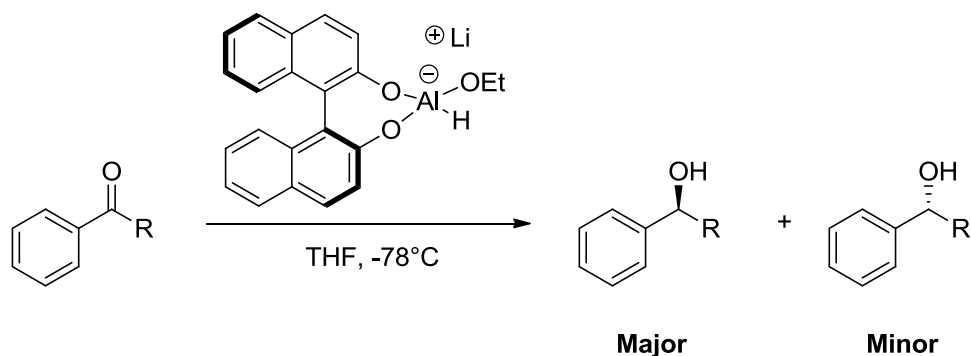


**Figure 1.3: Commonly encountered C<sub>2</sub>-symmetric ligands**

## 1.2 BINOL in Asymmetric Synthesis

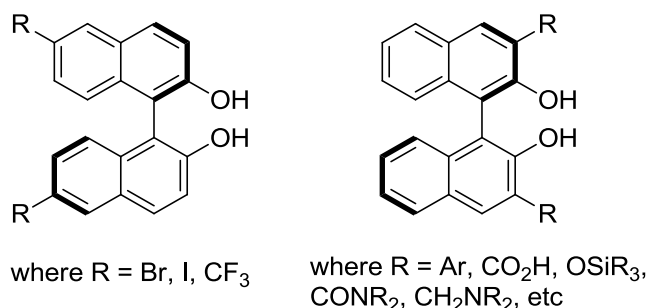
1,1'-Binaphthalene-2,2'-diol, more commonly referred to as BINOL, was first synthesized in 1926, long before its potential in asymmetric synthesis was first realized by Noyori in the reductions of aromatic aldehydes and ketones (Scheme 1.3).<sup>16</sup>





**Scheme 1.3: Asymmetric reduction by a BINOL-complex metal hydride**

BINOL itself is not always the best ligand for asymmetric synthesis, and much work has been done to modify and tune the ligand for optimal results in a wide variety of asymmetric reactions.<sup>17</sup> Various substitutions on the BINOLs can tune the electronic properties and change the steric environment of the ligand which is used for asymmetric induction in various reactions (Figure 1.4).<sup>18-23</sup> Many applications and modifications are noted in a review article by Yudin and co-workers.<sup>17</sup> More recently, a report entailing the use of chiral binaphtholate salts in enantioselective Mannich-type reactions has been reported.<sup>24</sup>



**Figure 1.4: Various substituted BINOL derivatives**

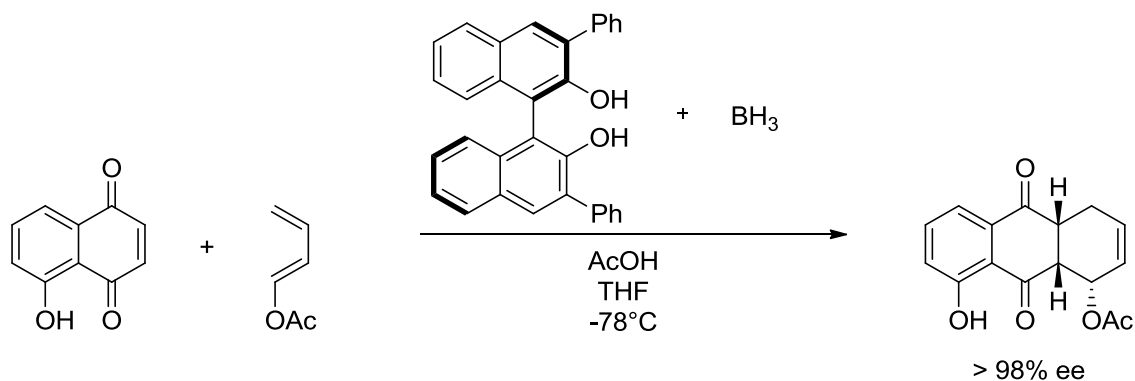
### 1.3 Boron in Asymmetric Synthesis

The electronic configuration of boron indicates that the maximum number of bonds that boron can have is four. Tetravalent boron, or borate salts, are shelf-stable compounds that are easy to

handle. Boron also forms strong covalent bonds with heteroatoms, for example O, N, and halogens.

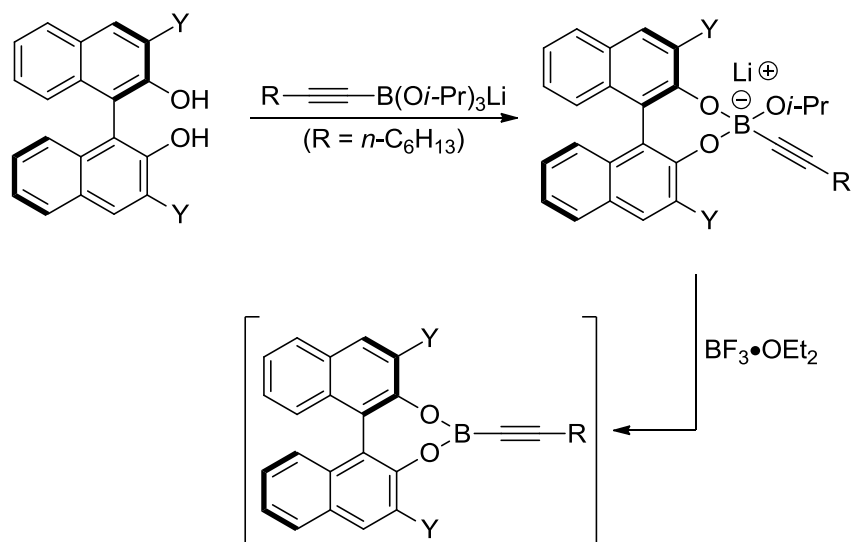
The seminal work by H.C. Brown and co-workers has demonstrated the versatility of organoboron compounds in organic synthesis.<sup>25</sup> The development of asymmetric syntheses using organoboranes began with asymmetric hydroboration and from this asymmetric reductions and later asymmetric allyl- and crotylboration were developed.<sup>25</sup> From here, advancements such as asymmetric reductions with Alpine-Borane<sup>®</sup> by Midland and co-workers and DIP-Chloride<sup>™</sup> by Brown pushed the envelope of organoboranes in asymmetric chemistry.<sup>26-30</sup> A review by Brown covers other asymmetric advances developed up until the early 1990's.<sup>31</sup>

Prior to 2000, few examples existed of asymmetric processes catalyzed specifically by binaphthol-modified boron compounds. Kelly reported a Diels-Alder reaction induced by a chiral binaphthol-boron complex (Scheme 1.4).<sup>32</sup> This chiral complex allows for predictable chirality of the product, high levels of enantiomeric excess and compatibility with a range of substrates.<sup>32</sup> Shortly thereafter, Yamamoto reported an asymmetric aza-Diels-Alder reaction catalyzed by a similar binaphthol-boron catalyst, affording products in up to 90% ee.<sup>33</sup>



**Scheme 1.4: Asymmetric Diels-Alder reaction catalyzed by a binaphthol-boron complex**

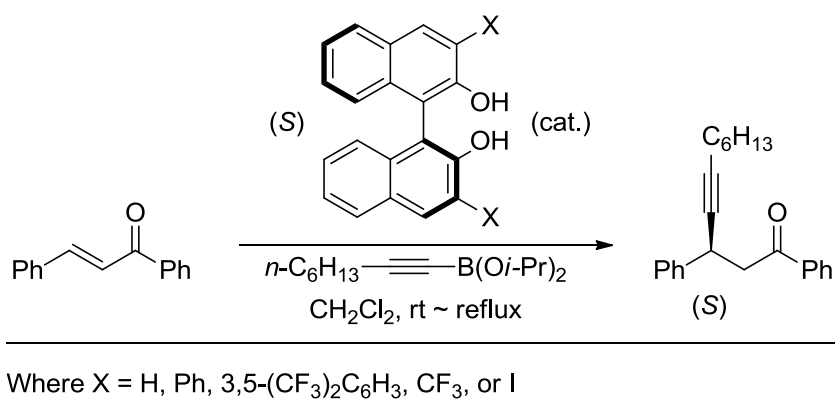
In 2000, Chong reported the first asymmetric alkynylboronations of enones using 3,3'-disubstituted binaphthol-modified boronates.<sup>34</sup> By adding a lithium alkynylborate salt to stoichiometric quantities of BINOL-substituted ligands in the presence of boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ), a binaphthol-substituted alkynylboronate was generated *in situ*, before the enone was added (Scheme 1.5).<sup>34</sup>



**Scheme 1.5: Preparation of the binaphthol alkynylboronate**

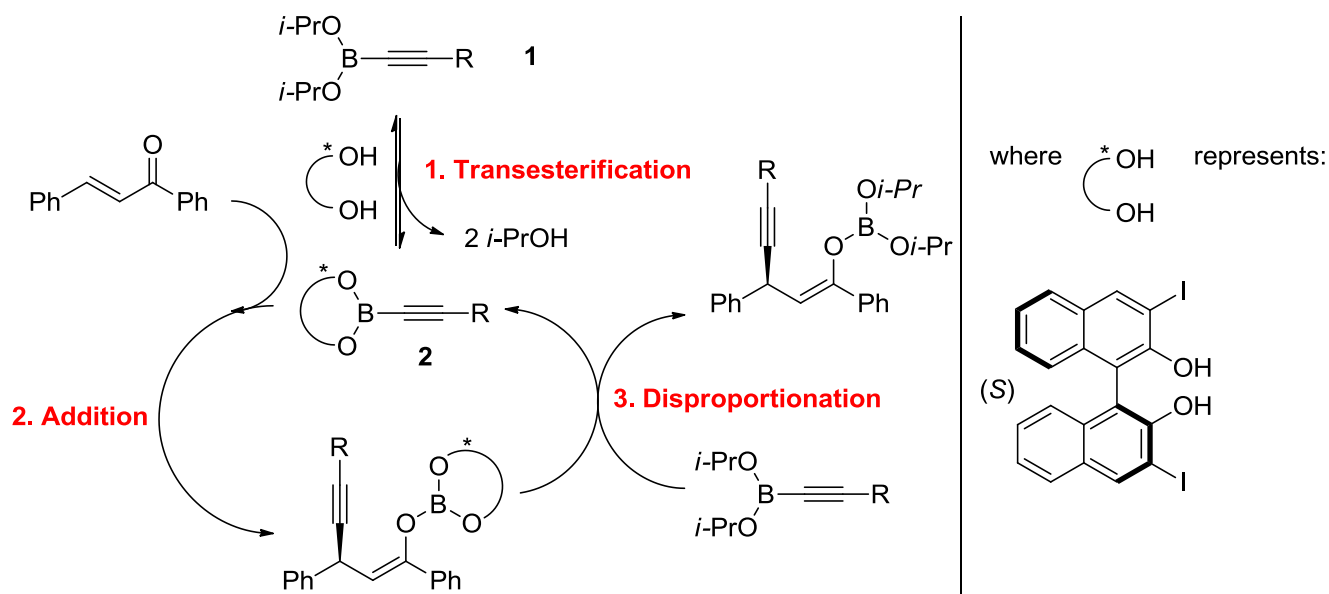
The yields and enantioselectivities were high for these reactions, with reported values up to 99% and 98%, respectively.<sup>34</sup> The stereochemistry of the reactions were found to coincide with the predicted stereochemistry based on a cyclic six-membered transition state, similar to the models proposed by Brown and by Noyori.<sup>35,36</sup> Two possible chair-like transition states are possible, with one of the transition states disfavoured due to steric interactions. This model was found to correlate strongly to the observed dependence on the size and electronic nature of the  $\beta$ -substituent of the enone.<sup>34</sup>

In 2004, the alkynylboration process was rendered catalytic.<sup>37</sup> Now, the alkynylboronate was transesterified with a chiral binaphthol ligand, forming a chiral boronate species that would undergo conjugate addition with an enone, transferring the alkynyl group from the boronate to the enone in the process (Scheme 1.6).<sup>37</sup>



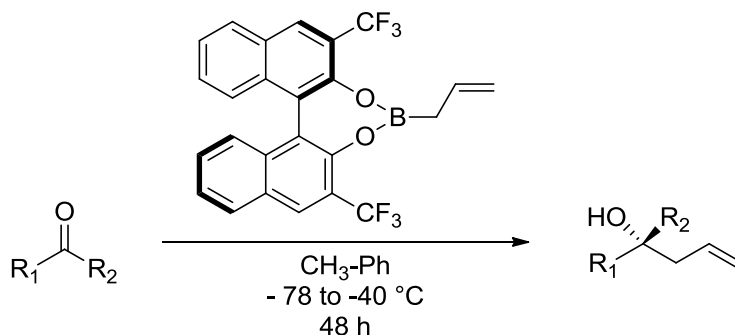
### Scheme 1.6: Asymmetric conjugate addition of an alkynylboronate to chalcone

The catalytic cycle turns, with the addition product trapped as a boron-enolate and the chiral diol is released to turn-over another addition (Scheme 1.7).<sup>37</sup> In order for the catalytic cycle to be effective, boronate **1** must be less reactive than boronate **2** towards the enone.<sup>37</sup>



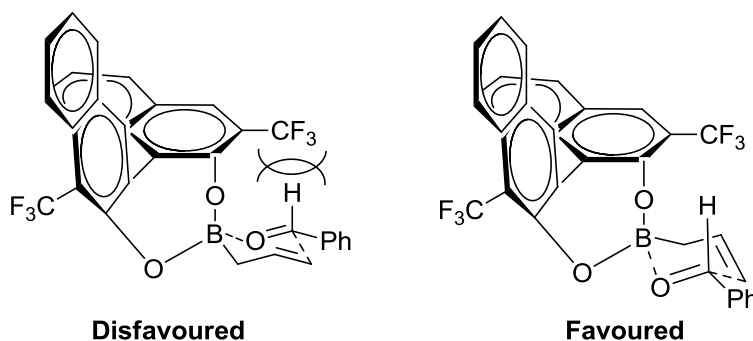
**Scheme 1.7: Proposed catalytic cycle**

In 2004, Chong and co-workers reported the asymmetric allylboration of aldehydes and ketones, using 3,3'-disubstituted BINOLs.<sup>38</sup> This chemistry expanded on previous allylations of aldehydes by Roush and co-workers, who made use of chiral diols derived from tartrates.<sup>39</sup> The allylboronates for these reactions were easily prepared by mixing triallylborane with the chiral binaphthol, followed by addition of aldehyde yielding the homoallylic alcohol (Scheme 1.8).<sup>38</sup>



**Scheme 1.8: Asymmetric allylation of aldehydes and ketones catalyzed by 3,3'-disubstituted binaphthol-modified boronates**

It was found that the CF<sub>3</sub>-substituted binaphthol gave both excellent yields and enantioselectivities.<sup>38</sup> The strongly electron-withdrawing nature of the CF<sub>3</sub> group makes the derived boronates more electrophilic and hence more reactive towards carbonyl compounds. Furthermore, the 3,3'-substituents play a role in destabilizing one of the possible transition states through a steric interaction between the binaphthol substituent and the smaller group of the carbonyl compound (Figure 1.5).<sup>38</sup>

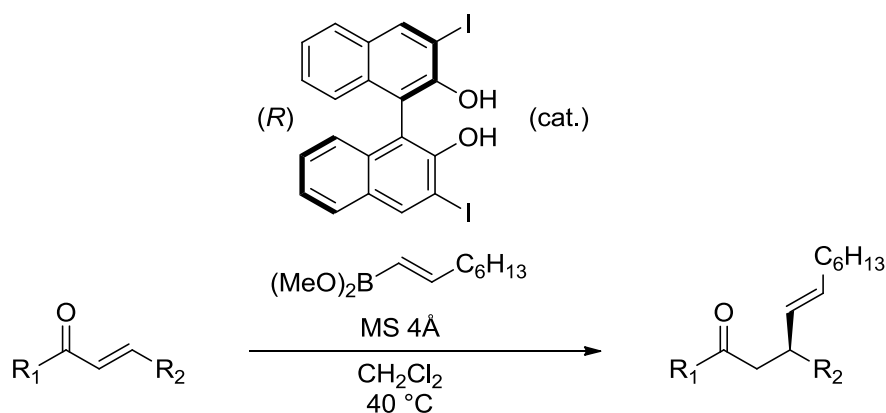


**Figure 1.5: Transition states for the asymmetric allylboration of aldehydes**

Allylboration of ketones were generally poor reactions; however, these conditions provided good yields and selectivities with ketone substrates, albeit with increased reaction times.<sup>38</sup> Ketones with two sterically different groups gave high selectivities, as better facial discrimination with the binaphthol-modified boronate occurred in these substrates.<sup>38</sup>

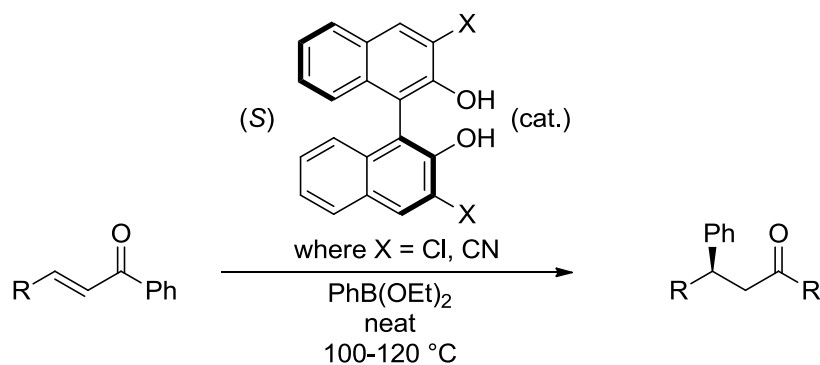
The substrate scope for the allylboration reaction was extended in 2006 to cyclic imines, yielding homoallylic amines in good yields.<sup>40</sup> Before this chemistry was introduced, there were few examples of asymmetric allylboration with acyclic imines and none with cyclic imines.<sup>40</sup> Again, as observed with the other chemistry the 3,3'-substituted binaphthols gave the best selectivities while the unsubstituted parent binaphthol gave very poor selectivity.<sup>40</sup>

The Chong group succeeded in the asymmetric conjugate alkenylboration and arylboration of enones catalyzed by chiral binaphthols in 2007 and 2011, respectively.<sup>41,42</sup> The conjugate alkenylation chemistry marked a breakthrough wherein a process had now been developed to transfer alkenyl groups to enones in the absence of transition-metal catalysts, using catalytic amounts of 3,3'-disubstituted binaphthols.<sup>41</sup> The alkenylboronates were easy to prepare, and transferred well to variety of enones (Scheme 1.9).<sup>41</sup> The enantioselectivities were rationalized using Zimmerman-Traxler transition states.<sup>41</sup>



**Scheme 1.9: Asymmetric conjugate alkenylboration of enones**

The conjugate arylboration proved to be difficult to develop. Initial conditions using up to 200 mol percent of the chiral binaphthol in non-polar, aprotic solvents such as dichloroethane, toluene, trifluorotoluene at temperatures up to 120 °C for extended times yielded only trace amounts of desired products.<sup>42</sup> Eventually, it was found that the optimal conditions were the treatment of the enone with 4 equivalents of arylboronate with catalytic amounts of binaphthols without additional solvent (Scheme 1.10).<sup>42</sup>

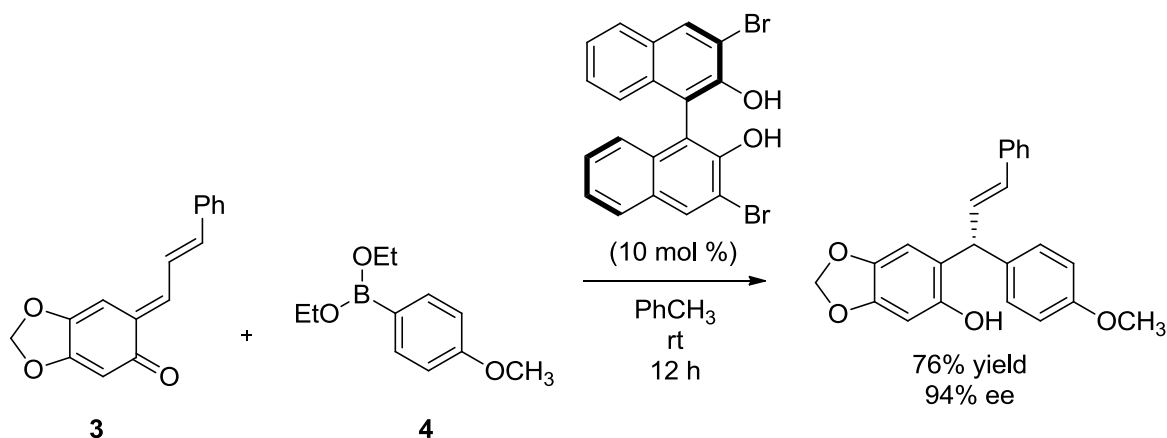


### Scheme 1.10: Asymmetric conjugate phenylboration of enones

The reaction was found to work best with 3,3'-dichlorobinaphthol and provided  $\beta,\beta'$ -aryl ketones in high yields and up to 99:1 enantioselectivity.<sup>42</sup> The enantioselectivities of the arylboration were also rationalized by Zimmerman-Traxler transition states.<sup>42</sup>

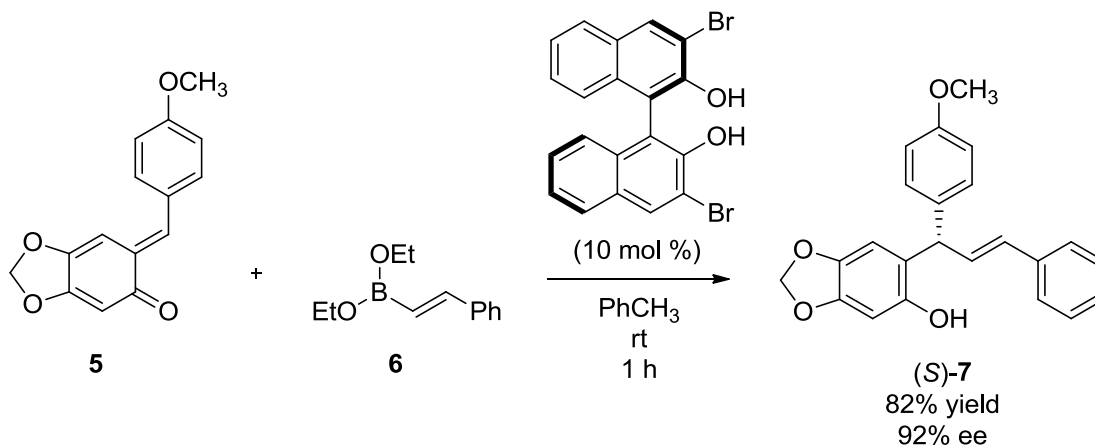
Later, Schaus expanded on binaphthol-catalyzed additions, similar to previous work from the Chong group.<sup>43-47</sup> Most recently, the Schaus group outlined the use of *o*-quinone methides (*o*-QMs), synthetic intermediates for hetero-Diels-Alder reactions, as substrates in the asymmetric additions of arylboronates and alkenylboronates.<sup>43</sup> In the addition of arylboronate **4** to *o*-QM **3**, various di-substituted BINOLs were screened, with 3,3'-dibromo-BINOL affording the greatest enantioselectivity (Scheme 1.11).<sup>43</sup>





**Scheme 1.11: Asymmetric arylation of *o*-quinone methides**

The group also evaluated the alkenylation of **6** with *o*-QM **5**, which provided the *S*-enantiomer **7** in shorter time, with a good yield and enantioselectivity (Scheme 1.12).<sup>43</sup>

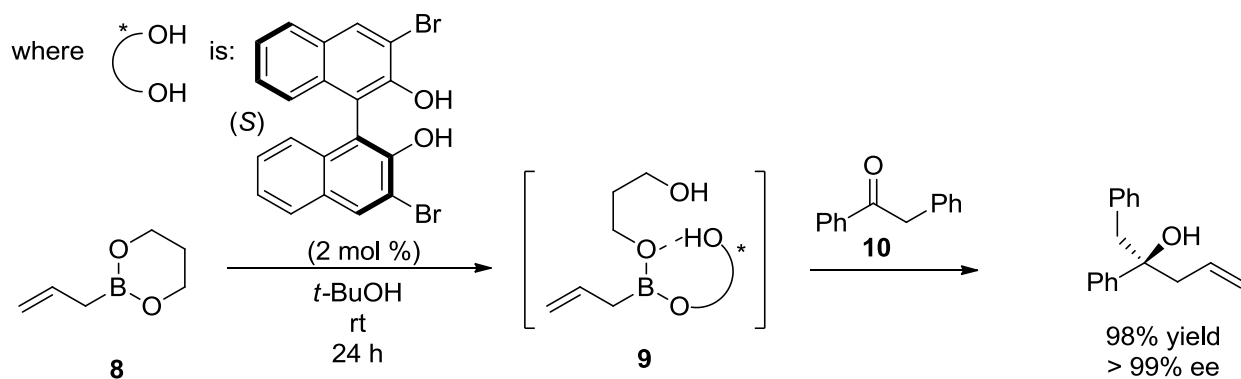


**Scheme 1.12: Asymmetric alkenylation of *o*-quinone methides**

In another report, Schaus's group examined the mechanism of the asymmetric allylboration of ketones catalyzed by 3,3'-disubstituted BINOLs.<sup>46</sup> With this mechanistic insight, they developed an improved reaction in solvent-free conditions at room temperature, affording enantiomerically pure compounds.<sup>46</sup> The new conditions use only 2 mol percent catalyst, compared to 15 mol

percent from their initial report, and were run at ambient temperature as opposed to  $-35\text{ }^{\circ}\text{C}$ .<sup>46,47</sup>

Both reactions possess similar mechanistic attributes, with a first-order rate dependence on catalyst concentration as well as binaphthol-boronate complex formation **9** (Scheme 1.13).<sup>46</sup>



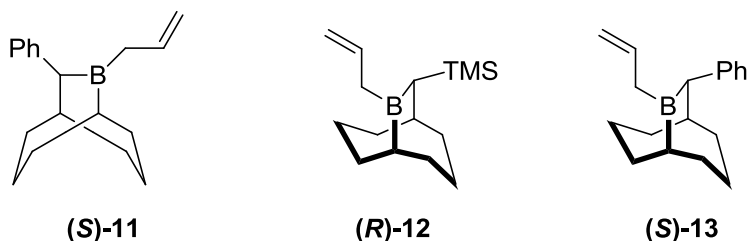
**Scheme 1.13: Asymmetric allylboration of ketones catalyzed by (S)-3,3'-Br<sub>2</sub>-BINOL**

*t*-BuOH (*tert*-butyl alcohol) was used as a non-coordinating alcohol to accelerate the catalyzed reaction, facilitating a ligand exchange without inhibiting the overall rate of reaction.<sup>46</sup>

Furthermore, the Schaus group have developed an asymmetric propargylation of ketones using allenylboronates catalyzed by chiral BINOLs, in solvent free conditions using microwave irradiation.<sup>44</sup> They have also found success with asymmetric additions of alkenyl and arylboronates to chromene acetals using other chiral ligands derived from tartaric acid, giving rise to chiral chromenes.<sup>45</sup>

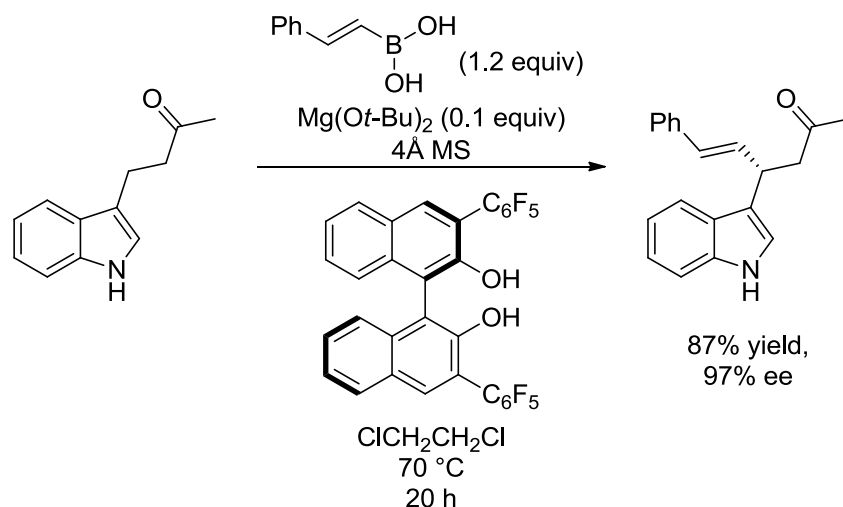
Soderquist and co-workers advanced the allylboration of ketones, reporting the use of chiral borabicyclo-decane reagents (**11**) for additions to dialkyl ketones containing pendant groups that are similar in size (Figure 1.6).<sup>48</sup> The reagents contain a built-in “chiral pocket” where the smaller group of the dialkyl ketone sits.<sup>48</sup> The conformation of the ketone creates two diastereotopic faces of the ketone for the addition, with one disfavoured due to steric

interactions.<sup>48</sup> The selectivities reported are higher than those of any previously known process.<sup>48</sup> Furthermore, the reagents are easily recycled at the end of the reactions for subsequent use.<sup>48</sup> Soderquist also reported additional borabicyclodecane reagents for the allylboration of *N*-trimethylsilyl ketimines (**12**) and *N*-triisopropylsilyl- $\alpha$ -amino aldehydes (**13**) (Figure 1.6).<sup>49,50</sup> These reagents contain a similar chiral pocket to the reagents for allylboration of ketones, and provide tertiary carbamines or *O*-triisopropylsilyl- $\beta$ -amino alcohols respectively with good enantioselectivities.<sup>49,50</sup>



**Figure 1.6: Soderquist's borabicyclodecane reagents for allylboration**

In 2011, May and co-workers reported the additions of alkenylboronic acids and alkynylboronic esters to indole-appended enones in the presence of 3,3'-bis(pentafluorophenyl)-BINOL (Scheme 1.14).<sup>51</sup> The addition of Mg(*Ot*-Bu)<sub>2</sub> (magnesium *tert*-butoxide) as an additive was found to improve the reaction, however, its role in the reaction remains unknown.<sup>51</sup>



**Scheme 1.14: Additions of alkenylboronic acids to indole-appended enones**

Subsequently, the group reported additions of vinyl boronic acids to unprotected heterocyclic-appended enones using 3,3'-bis(perfluorophenyl) BINOL, forming allylic and propargylic stereocenters in good enantioselectivities.<sup>52</sup> The heterocyclic cores of the enones found compatible included furans, thiophenes, pyridines, quinolines, pyrazines, thiazoles, pyrroles, indoles, and imidazoles.<sup>52</sup>

## Chapter 2: Fluorine in Synthetic Chemistry

### 2.1 Properties of the Trifluoromethyl Group

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Bioisosteres are compounds that are structurally distinct, yet recognized similarly by biological systems.<sup>53</sup> Bioisosteres are commonly not exact structural mimetics but instead more alike in biological rather than physical properties.<sup>53</sup> Bioisostere design can also introduce structural changes in the molecule that can be either beneficial or detrimental depending on the size, shape, electronic distribution, polarizability, dipole, polarity, lipophilicity and pK<sub>a</sub>.<sup>54</sup> Some examples of classical bioisosteres are highlighted below in Table 2.1.<sup>53</sup>

**Table 2.1: Classical monovalent bioisosteres**

Monovalent Bioisosteres	
D and H	F and H
NH and OH	RSH and ROH

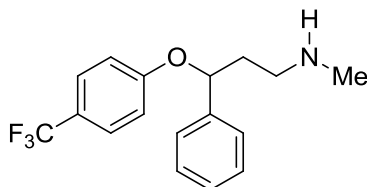
Fluorine was initially chosen as a bioisostere to H with hopes that it would interfere with metabolic processes, a key strategy that is now commonly employed in lead drugs.<sup>54</sup> Metabolic stability is a key factor in determining the bioavailability of a compound.<sup>54</sup> The rapidly occurring oxidative metabolism that takes place in the liver by the cytochrome P450 enzymes has been found to limit bioavailability.<sup>54</sup> A common strategy to circumvent this is to substitute a C-H bond which may be oxidized for a C-F bond which cannot, thus increasing the metabolic stability of the compound.<sup>54</sup> Fluorine has also been found to decrease the basicity of functional groups when placed in close proximity, thus resulting in better membrane permeability of a compound and increasing its bioavailability.<sup>54</sup> The fluorine atom of the highly polarizable C-F bond can participate in weak hydrogen bonding only.<sup>57</sup> Fluorine strongly bonds to carbon, with

a bond dissociation energy of approximately  $105 \text{ kcal mol}^{-1}$ .<sup>55-58</sup> Additionally, fluorine's participation in electrostatic interactions is hypothesized to contribute to the increased binding affinity of fluorinated analogues for an enzyme's active site.<sup>57</sup> More specifically, in a series of thrombin inhibitors, measurement of the log *D* value showed that an increase in lipophilicity alone could not describe the increased binding affinity of a fluorinated analogue, which was considerably more active.<sup>57</sup> X-ray crystallographic analysis uncovered the presence of electrostatic interactions between the C-F bond and C=O and H-C<sub>α</sub> unit of Asn98 in the active site.<sup>57</sup> These observations support the notion the C-F bond of fluorinated analogues participates in electrostatic interactions, which in turn contributes to an increase in binding affinity.

The substitution of a fluorine for hydrogen has little steric effect and is commonly accepted in biologically active molecules due to the similarity in the van der Waals radius of fluorine (1.47 Å) to oxygen (1.57 Å) and hydrogen (1.20 Å).<sup>57</sup> This small change accounts for the minor steric bulk fluorine produces in the active site of biological receptors.<sup>57</sup> The trifluoromethyl group on the other hand may dictate a steric change as it is commonly estimated to be close in size to an ethyl group, although possessing a much different 3D geometry, which may precipitate a different preferred molecular orientation.<sup>55</sup> The conformational energy (A-value) or difference in energy between the axial and equatorial substituent on a monosubstituted cyclohexane is 2.8 kcal mol<sup>-1</sup> for the trifluoromethyl group, which is closer in value to that of the isopropyl group (2.21 kcal mol<sup>-1</sup>), than that of an ethyl or methyl group is (1.79 and 1.74 kcal mol<sup>-1</sup>, respectively).<sup>59</sup> An example of the electronic modification of the fluorine bioisostere is revealed in 1,2-difluoroethane. 1,2-Difluoroethane is known to prefer a *gauche* conformation, as opposed to the commonly observed *anti* orientation with 1,2-substituents on other di-substituted ethanes.<sup>57</sup> In the *gauche* conformation, both fluorine atoms are antiperiplanar to a C-H bond, and

adopt a conformation that benefits from a stabilizing hyperconjugative interaction of the C-H  $\sigma$  bond to the C-F  $\sigma^*$  orbital.<sup>57</sup>

The antidepressant fluoxetine sold by Eli Lilly under the name Prozac<sup>®</sup> possesses the CF<sub>3</sub> functional group on one of the aryl rings (Figure 2.1).<sup>57</sup>



**Figure 2.1: Structure of Prozac<sup>®</sup>**

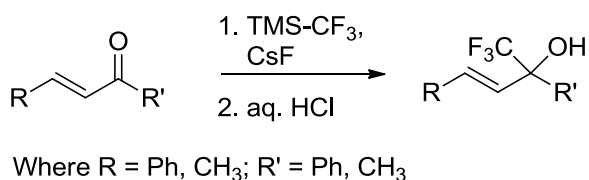
First approved for sale by the Food and Drug Administration (FDA) in 1987, Prozac<sup>®</sup> has become one of the most prescribed antidepressants worldwide.<sup>57</sup> Studies have indicated that depression is linked to low levels of serotonin, a neurotransmitter.<sup>57</sup> Prozac<sup>®</sup> works to inhibit the re-uptake of serotonin allowing the neurotransmitter to concentrate and activate its specific receptor.<sup>57</sup> Studies on the structure-activity relationship revealed that the trifluoromethyl group in the *para*-position of the phenolic ring specifically increased the inhibition potency of serotonin by 6-fold compared to the non-fluorinated parent compound.<sup>60</sup> It is hypothesized that due to the steric bulk of the CF<sub>3</sub> group, the phenolic ring adopts a specific orientation.<sup>61</sup> This orientation is critical for recognition of the inhibitor by the serotonin transporter, due to interactions between residues of the inhibitor and domains of the transporter.<sup>61</sup> These interactions provide sites of recognition for the transporter to bind the inhibitor with increased affinity.<sup>61</sup>

## 2.2 Recent Strategies in Trifluoromethylation Chemistry

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The Ruppert-Prakash reagent  $\text{Me}_3\text{SiCF}_3$ , more commonly called Ruppert's reagent, was first reported in 1984 and has significantly contributed to the advancement of nucleophilic trifluoromethylation of organic substrates.<sup>62</sup> This reagent was first used in the nucleophilic addition of the  $\text{CF}_3$  group to carbonyls by Prakash and co-workers in 1989.<sup>63</sup> Nucleophilic trifluoromethylation with Ruppert's reagent was classically initiated by a nucleophilic fluoride source, often in the form of either potassium fluoride (KF) or tetrabutylammonium fluoride (TBAF).<sup>64</sup>

More relevant to our research is the nucleophilic trifluoromethylation of enones with Ruppert's reagent, which has been demonstrated to proceed regioselectively. Reacting either a cyclic or acyclic enone in the presence of a catalytic amount of fluoride proceeds in a nucleophilic 1,2-addition of the  $\text{CF}_3$  moiety to the carbonyl carbon, affording the corresponding trifluoromethylated alcohols after hydrolytic work-up (Scheme 2.1).<sup>65</sup> No 1,4-addition was observed under the reported reaction conditions.

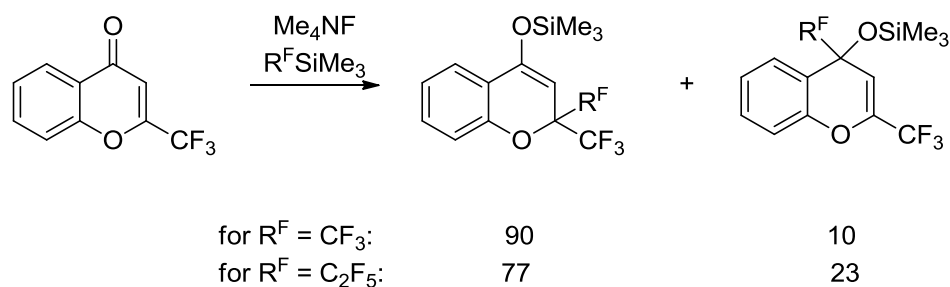


**Scheme 2.1: Nucleophilic 1,2-addition of  $\text{CF}_3$  to *trans*-enones**

Recently, Prakash and co-workers reported a synthesis of Ruppert's reagent from fluoroform,  $\text{CF}_3\text{H}$ , using lithium hexamethyldisilazide (LHMDS).<sup>66</sup> Subsequently, they demonstrated that the generation of Ruppert's reagent *in situ* can be used in racemic 1,2-additions to a range of substrates.<sup>66</sup>



Nucleophilic 1,4-addition of the trifluoromethyl group was first accomplished by Sosnovskikh on chromone derivatives, using a fluoride ion as the initiator in the  $\text{CF}_3$  transfer.<sup>67</sup> Additions using larger nucleophiles such as the  $\text{C}_2\text{F}_5$  group with  $\beta$ -substituted chromones resulted in a decrease in the regioselectivity, with 1,2-addition products also formed (Scheme 2.2).<sup>67</sup>

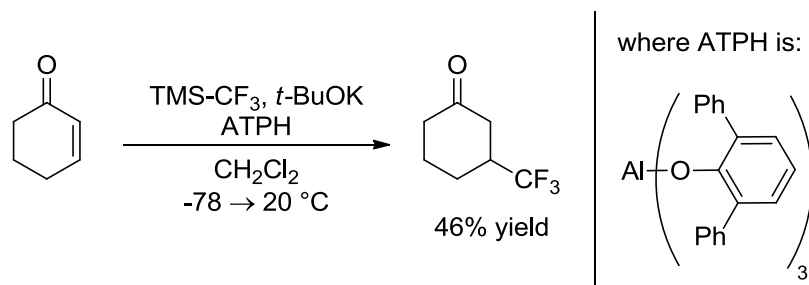


**Scheme 2.2: 1,4-addition of  $\text{CF}_3$  and  $\text{C}_2\text{F}_5$  to chromone derivatives**

Other nucleophilic sources such as alkoxides, amine *N*-oxides, acetates, carbenes and phosphines, have been used to initiate the nucleophilic trifluoromethylation of various functional groups.<sup>68-77</sup>

Based on this work, early strategies were developed towards the regioselective 1,4-addition of a trifluoromethyl group to  $\alpha,\beta$ -unsaturated enones. Sevenard and co-workers initially attempted to generate a copper- $\text{CF}_3$  species by mixing Ruppert's reagent/ $\text{Me}_4\text{NF}/\text{CuI}$  in THF, which furnished exclusively the 1,2-addition product.<sup>78</sup> Subsequently, they attempted to prepare a "pre-generated"  $\text{CuCF}_3$  species with DMF/NMP (*N*-methyl-2-pyrrolidinone), which yielded a mixture of unidentified products.<sup>78</sup> By first treating the substrate with a bulky aluminum-based Lewis acid, followed by the addition of Ruppert's reagent and a nucleophilic initiator, the 1,4-addition product was exclusively obtained (Scheme 2.3).<sup>78</sup> At the time, this *in situ* protection followed by

addition was the only synthetic method to generate  $\beta$ -trifluoromethyl carbonyl compounds on a preparative scale.<sup>78</sup>



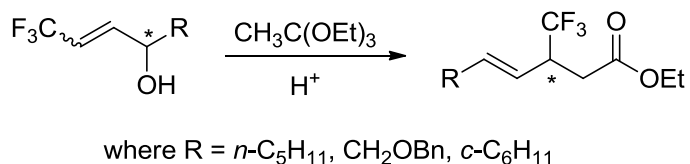
### Scheme 2.3: Regioselective conjugate addition of the trifluoromethyl group

Further studies have revealed that substrates such as arylidenemalononitriles and arylidene Meldrum's acids can undergo nucleophilic conjugate trifluoromethylation with Ruppert's reagent.<sup>79,80</sup> Other recent reagents for nucleophilic trifluoromethylations are highlighted in a review article by Langlois.<sup>81</sup>

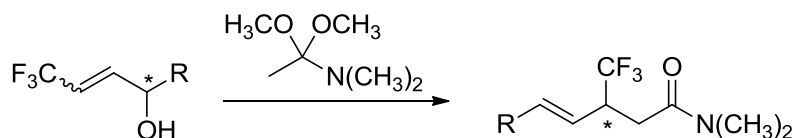
Asymmetric trifluoromethylation of interesting substrates including amino acids, steroids, carbohydrates, inositol derivatives, sulfinimines and aziridines have been covered in a review article by Ma and Cahard.<sup>82</sup> Since this review, recent work involving the asymmetric trifluoromethylation of chiral *N*-sulfinylimines, 2-acyl-1,3-perhydrobenzoxazines, and chiral  $\alpha$ -keto esters and sulfonyl groups has been accomplished.<sup>83-86</sup>

Although many strategies have been developed to prepare chiral  $\beta$ -trifluoromethyl ketones, none of them include asymmetric conjugate additions of a trifluoromethyl group to an  $\alpha,\beta$ -unsaturated enone. In 1997, Kitazume and co-workers detailed the Johnson-Claisen and Eshenmoser-Claisen rearrangements of chiral  $\gamma$ -trifluoromethylated allylic alcohols which were prepared by an effective enzymatic resolution of the corresponding propargylic alcohols (Scheme 2.4).<sup>87</sup>

### Johnson-Claisen Rearrangement

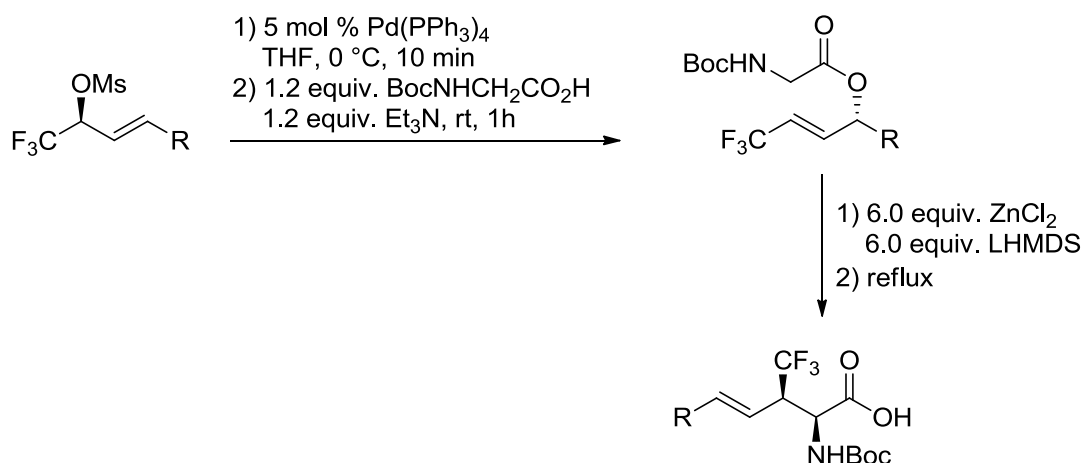


### Eshenmoser-Claisen Rearrangement



### Scheme 2.4: Stereoselective synthesis of CF<sub>3</sub> compounds by sigmatropic rearrangements

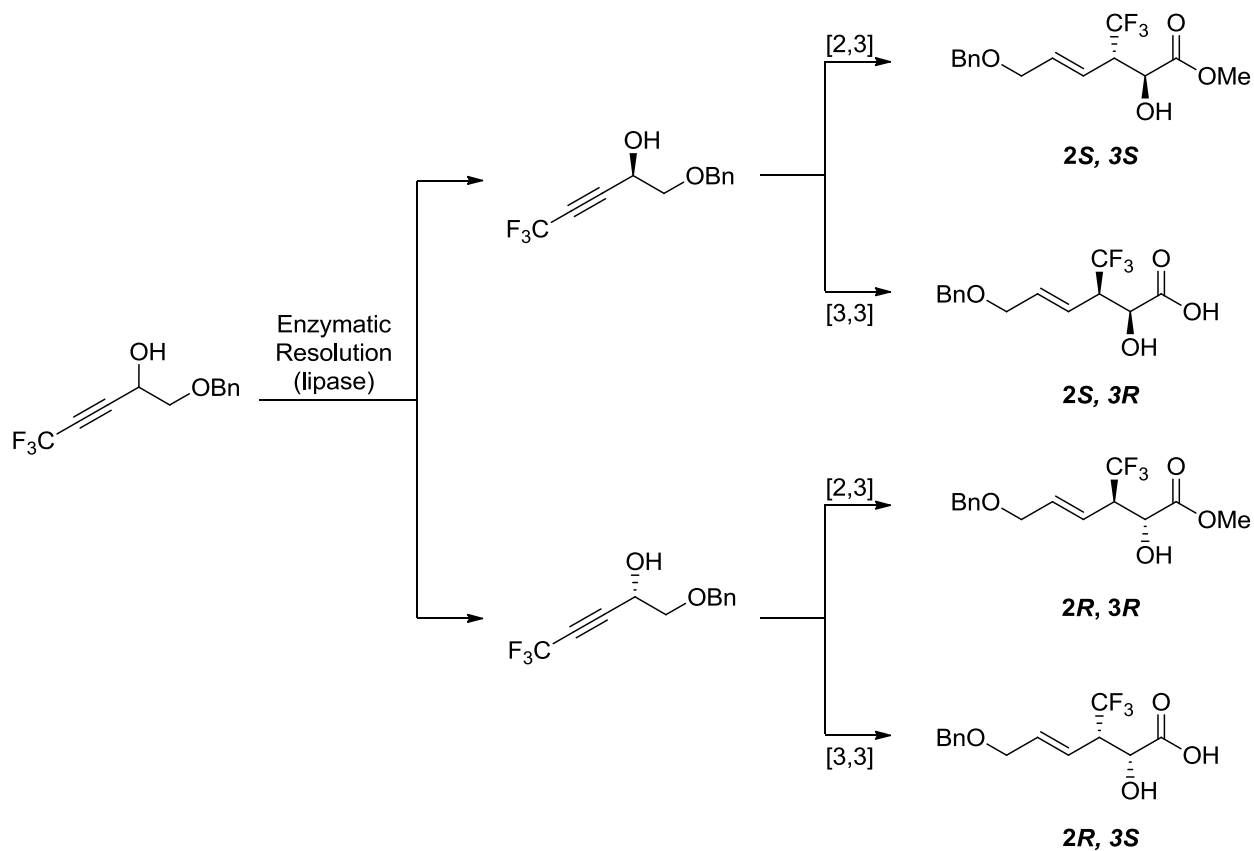
Similarly, Konno and co-workers similarly published a report of allylic substitution reactions of different chiral  $\alpha$ -fluoroalkylated mesylates with carboxylic acids in the presence of a palladium catalyst to furnish  $\gamma$ -fluoroalkylated allyl esters in excellent yields.<sup>88</sup> These esters were subjected to an Ireland-Claisen rearrangement to provide homochiral  $\beta$ -fluoroalkylated- $\gamma$ - $\delta$ -unsaturated amino acids in good yields (Scheme 2.5).<sup>88</sup>



### Scheme 2.5: Synthesis of $\alpha$ -fluoroalkylated- $\beta$ - $\gamma$ -unsaturated amino acids

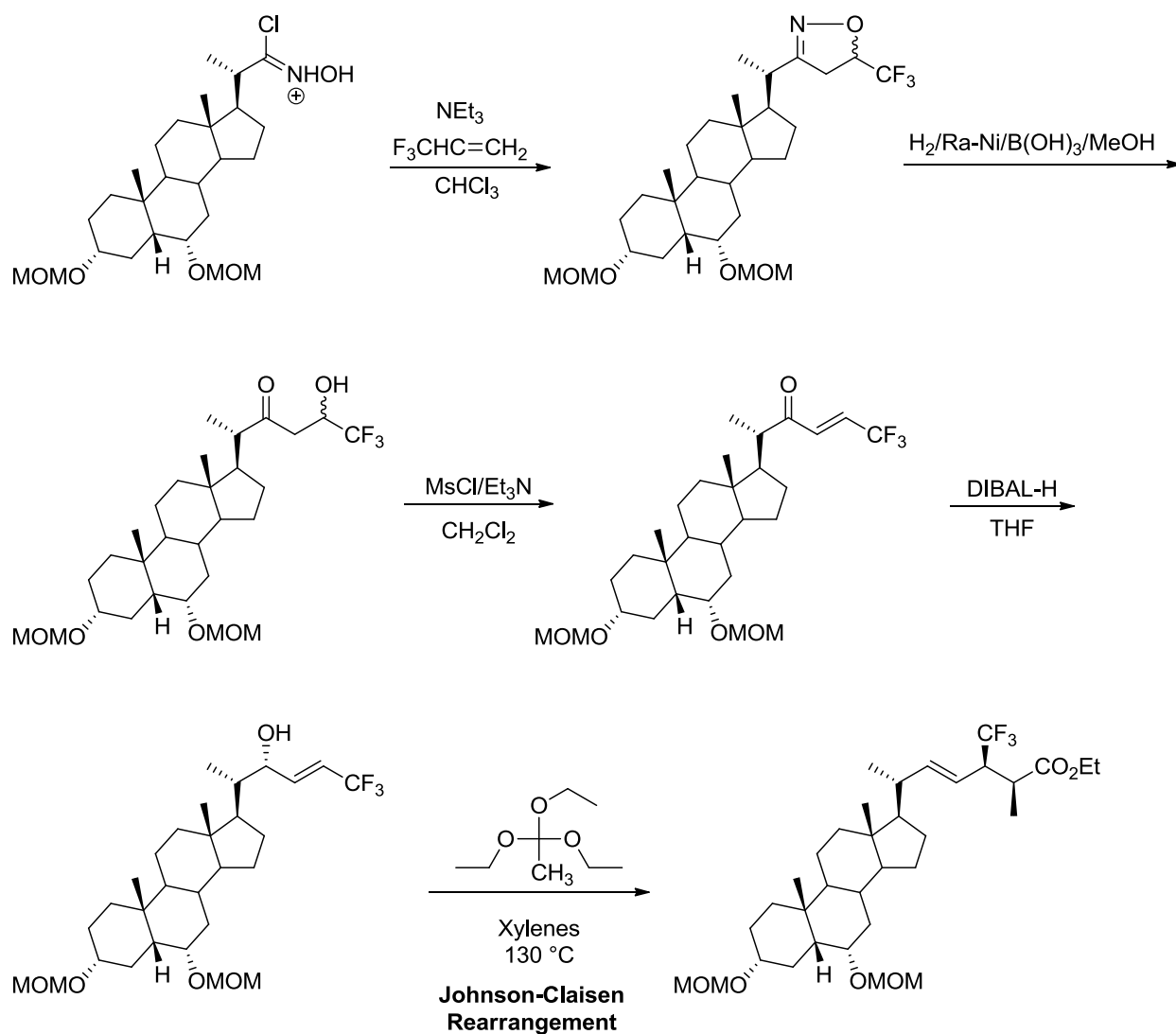
Subsequently, the group published a report wherein the products from the [3,3]-Ireland-Claisen rearrangement were subjected to iodolactonization followed by osmylation for the synthesis of  $\gamma$ -lactones with four contiguous stereocenters.<sup>89</sup>

Konno and co-workers further investigated ester-enolate [2,3]-Wittig and [3,3]-Ireland-Claisen rearrangements of various substrates to prepare trifluoromethylated compounds bearing two contiguous stereocenters.<sup>90</sup> By starting with a racemic propargyl alcohol, an effective enzymatic kinetic resolution was used to obtain enantiomerically pure propargylic alcohols which were subjected to either the [2,3]-Wittig or [3,3]-Ireland-Claisen rearrangements (Scheme 2.6).<sup>90</sup>



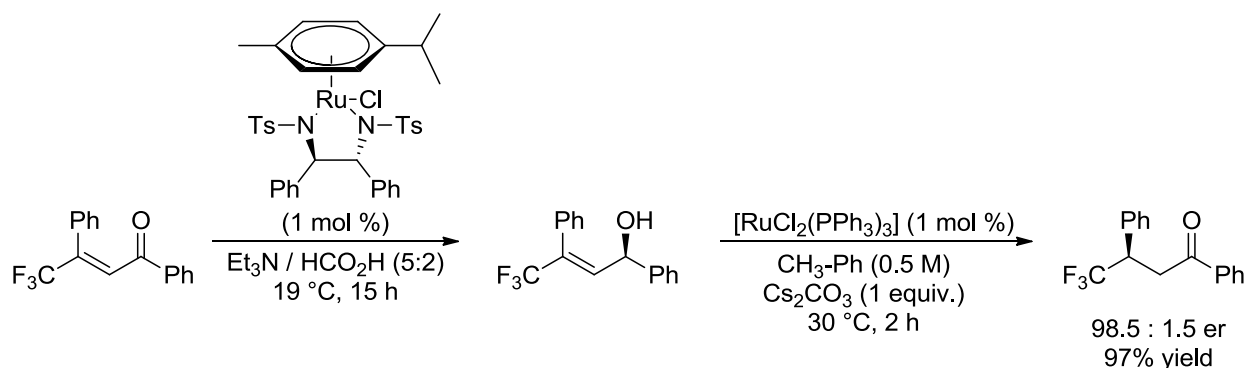
**Scheme 2.6:** [2,3]-Wittig and [3,3]-Ireland-Claisen rearrangements of propargylic alcohols

Jiang and co-workers reported a pathway towards the 22*E*,24β(*S*)-CF<sub>3</sub> side chain of sterols by use of a 1,3-dipolar cycloaddition and stereocontrolled Johnson-Claisen rearrangement.<sup>91</sup> Through the series of transformations, the group was able to prepare chiral trifluoromethyl-substituted sterols (Scheme 2.7).<sup>91</sup>



**Scheme 2.7: 1,3-dipolar cycloaddition and Johnson-Claisen rearrangement of CF<sub>3</sub>-substituted sterols**

Renaud and Cahard recently published the ruthenium-catalyzed redox isomerization of trifluoromethylated allylic alcohols as a method for preparing enantioenriched carbonyl compounds containing a  $\beta$ -trifluoromethyl group.<sup>92</sup> The group was able to generate material in near-quantitative yield and in excellent enantioselectivity (Scheme 2.8).<sup>92</sup>



**Scheme 2.8: Enantiospecific redox-isomerization of  $\beta$ -trifluoromethyl enones**

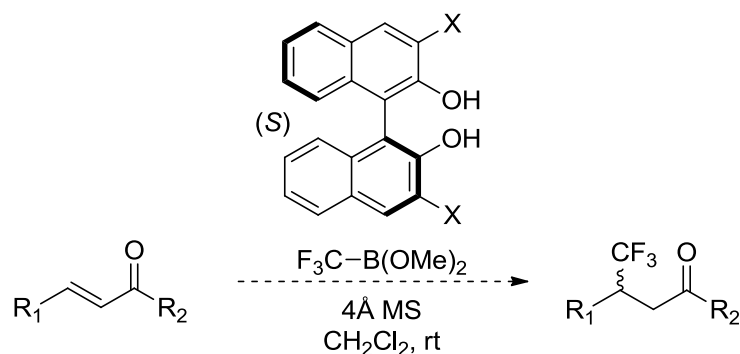
Other chemistry related to fluorination in medicinal chemistry, with respect to electrophilic and enantioselective monofluorination processes are covered along with recent applications of fluorine chemistry in drugs in a brief review by Kirk.<sup>93</sup>

## Chapter 3: Developing the Asymmetric Conjugate Trifluoromethylation of Enones

### 3.1 Preparation of Trifluoromethylboronates

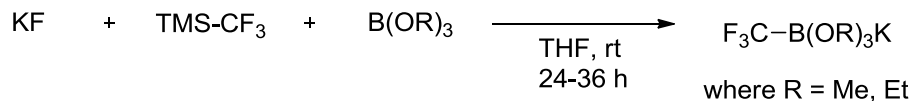
Currently, there are few literature precedents for the conjugate addition of the trifluoromethyl group to  $\alpha,\beta$ -unsaturated substrates. Furthermore, there are no reported methods for the asymmetric conjugate addition of the trifluoromethyl group. The goal of this work is to develop a new methodology to introduce the trifluoromethyl moiety into  $\alpha,\beta$ -unsaturated compounds.

This work will be based extensively on the previous methods of binaphthol-catalyzed asymmetric conjugate additions developed by the Chong lab. The initial focus will be towards the synthesis of a trifluoromethyl boronate, which will be screened in the proposed reaction scheme illustrated below (Scheme 3.1).



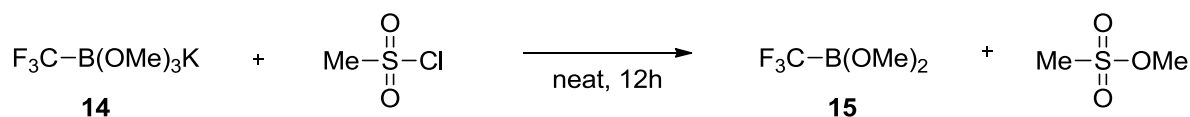
**Scheme 3.1: Proposed asymmetric conjugate trifluoromethylation**

In 2003, Kolomeitsev and co-workers published a report that detailed the preparation of perfluoroalkyl borates for use in Suzuki and Petasis reactions.<sup>94</sup> The group prepared a range of perfluoroalkyl trialkoxyborate salts in quantitative yields via a simple one-step reaction.<sup>94</sup> Most relevant to our objective was the preparation of potassium trifluoromethyl trimethoxyborate (Scheme 3.2).<sup>94</sup>



### Scheme 3.2: Synthesis of potassium trifluoromethyl trialkoxyborates

With the potassium trifluoromethyl trimethoxyborate salt in hand, Kolomeitsev's group then dealkoxylated the salts with various electrophiles, yielding previously unknown trifluoromethylboronates.<sup>94</sup> Most relevant to our work was the preparation of dimethyl trifluoromethyl boronate **15**, by reacting trifluoromethyl borate salt **14** with mesyl chloride (Scheme 3.3).<sup>94</sup>

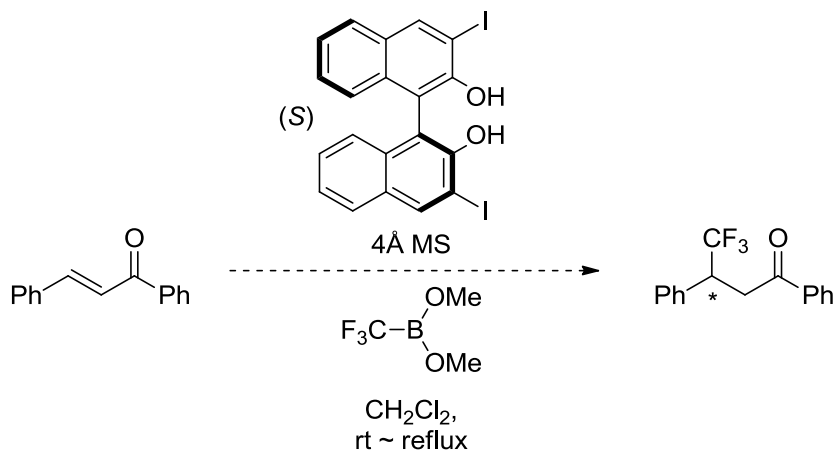


### Scheme 3.3: Preparation of trifluoromethylboronate 15

Other electrophiles used for the dealkoxylation included methyl trifluoromethanesulfonate, trimethylsilyl chloride and tolyl trifluoromethanesulfonate.<sup>94</sup>

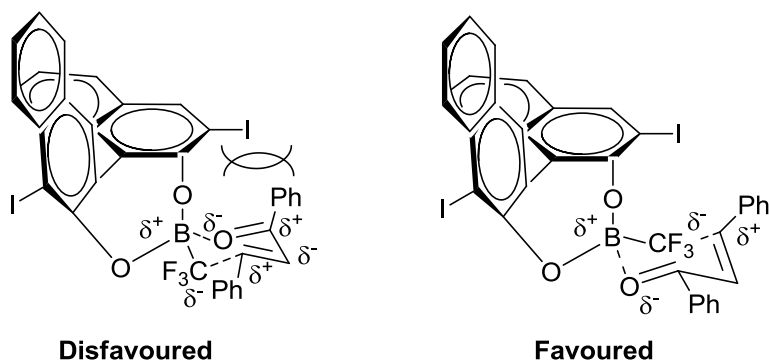
With the dimethyl trifluoromethylboronate in hand, we plan to examine its reactivity in the binaphthol-catalyzed asymmetric conjugate additions to enones (Scheme 3.4). 3,3'-disubstituted BINOLs will be prepared according to literature procedures, with 3,3'-diiodo-BINOL initially used due to its success in the asymmetric conjugate alkynylations developed by the Chong group.<sup>37</sup>





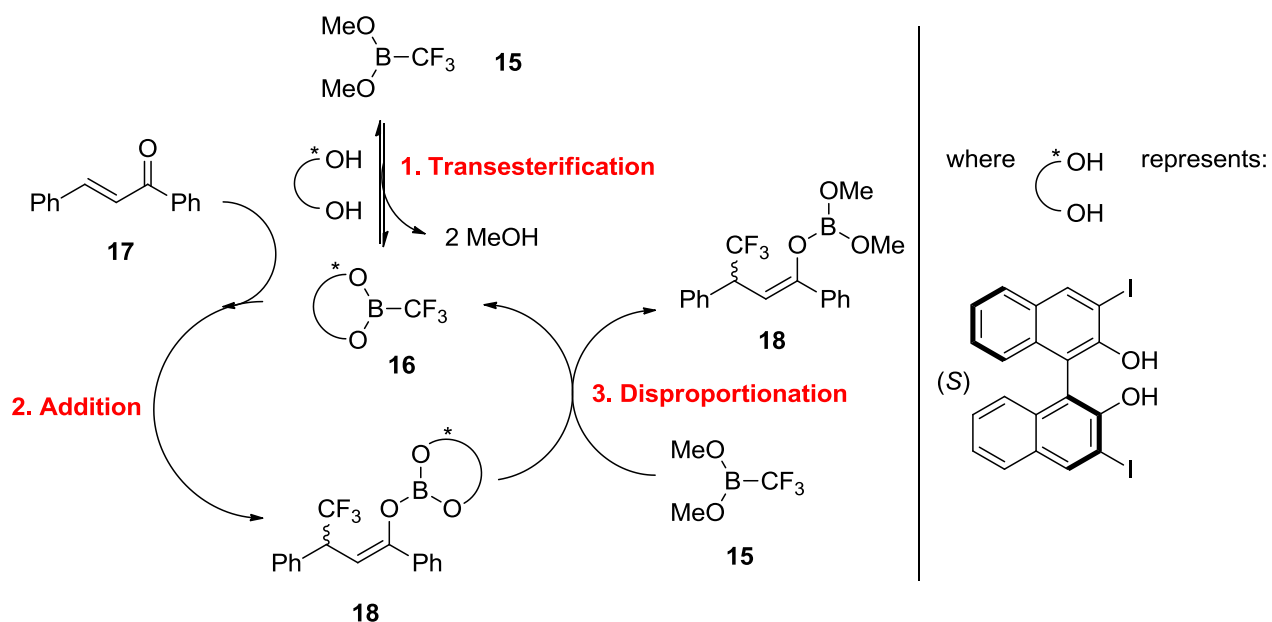
**Scheme 3.4: Proposed asymmetric conjugate trifluoromethylboration of chalcone**

The trifluoromethylation chemistry was expected to proceed similarly to the alkynylboration chemistry previously reported, primarily due to the similarities in the water-based pKa's of fluoroform and acetylene (27 and 24, respectively).<sup>95,96</sup> The trifluoromethyl group should stabilize the developing negative charge in the transition state, which in turn lowers the energy of the transition state, decreasing the energy barrier for the reaction to occur. The expected enantioselectivities can also be rationalized using Zimmerman-Traxler models, with one of the diastereomeric transition states disfavoured due to steric interactions of the BINOL with the phenyl group of the enone situated in the pseudo-axial conformation (Scheme 3.5).



**Scheme 3.5: Zimmerman-Traxler transition states with developing charges shown**

The catalytic cycle for the trifluoromethylboration should loosely correlate with the alkynylboration, and can be adopted from a report published by Goodman rationalizing the catalytic cycle for the conjugate alkynylation.<sup>97</sup> In order for the catalytic cycle to proceed, the energy barrier for the reaction of **15** with **17** must be higher than that of **16** with **17** (Scheme 3.6).<sup>97</sup> The boronate also binds tightly to the enone, activating it for the reaction.<sup>97</sup> The calculated values from the theoretical study on the alkynylation revealed the boron-oxygen bond length in the transition state with **16** is smaller than that with **15**. Additionally, formation of a complex between **16** and **17** lowers the energy of the LUMO of the enone, facilitating the conjugate addition reaction.<sup>97</sup>



**Scheme 3.6: Catalytic cycle for the trifluoroboration of chalcone with 3,3'-diiodo-BINOL**

Electron withdrawing 3,3'-substituents on the BINOL increase the Lewis acidity of the boron by withdrawing electron density from the oxygen atoms. The electrons on the oxygen atoms are also delocalized into the adjacent aromatic systems, lowering their ability to donate into boron's

vacant orbital. Additionally, the lone pairs of the oxygen atoms are not spatially oriented to interact with the empty orbital of boron. These factors effectively increase the Lewis acidity of the boron, and facilitate co-ordination of the boron to the carbonyl oxygen of the enone, promoting the likelihood for the conjugate addition to take place, forming **18**.

If the initial studies using the 3,3'-diiodo BINOL prove to be unsuccessful, one can tune the BINOL ligands to either reduce any steric interactions in the transition state, or to electronically activate the chiral boronate complex's co-ordination with the enone (**16** in Scheme 3.6). One could turn to the 3,3'-(CN)<sub>2</sub>-BINOL, for example, which has a greater  $\sigma$ -substituent constant compared to iodine, which should in turn accelerate the reaction due to an increase in the Lewis acidity of complex **16**.

If these modifications prove unsuccessful, the next step would be to move from using catalytic quantities of the BINOL to stoichiometric amounts. Although more of the binaphthol would be added in the reactions, it could easily be recovered and recycled for subsequent reactions.

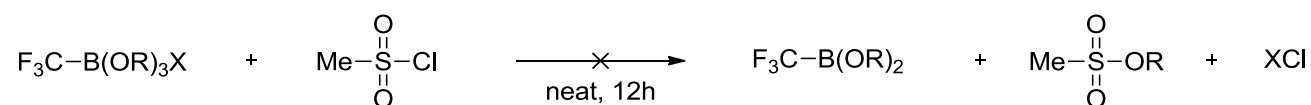
### 3.2 Results and Discussion

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Efforts to obtain the dimethyl trifluoromethyl-boronate began by following the procedure outlined by Kolomeitsev *et al.*<sup>94</sup> Obtaining appreciable quantities of the potassium trifluoromethyl trimethoxy borate was straightforward. However, the subsequent step which required treating the borate with methanesulfonyl chloride to furnish the dimethyl trifluoromethylboronate was unsuccessful even after repeated attempts. The isolation of the dimethyl trifluoromethylboronate was unsuccessful, as the compound is both volatile and unstable.

Despite these initial failures, the focus was shifted towards synthesizing other dialkyl trifluoromethyl boronates which were believed to confer additional stability to the boronate. Following the same procedure, the synthesis of both the potassium triisopropoxy trifluoromethyl borate and the potassium triethoxy trifluoromethyl borate salts were successful. However, the subsequent de-alkoxylation of these borate salts failed despite repeated attempts (Table 3.1).

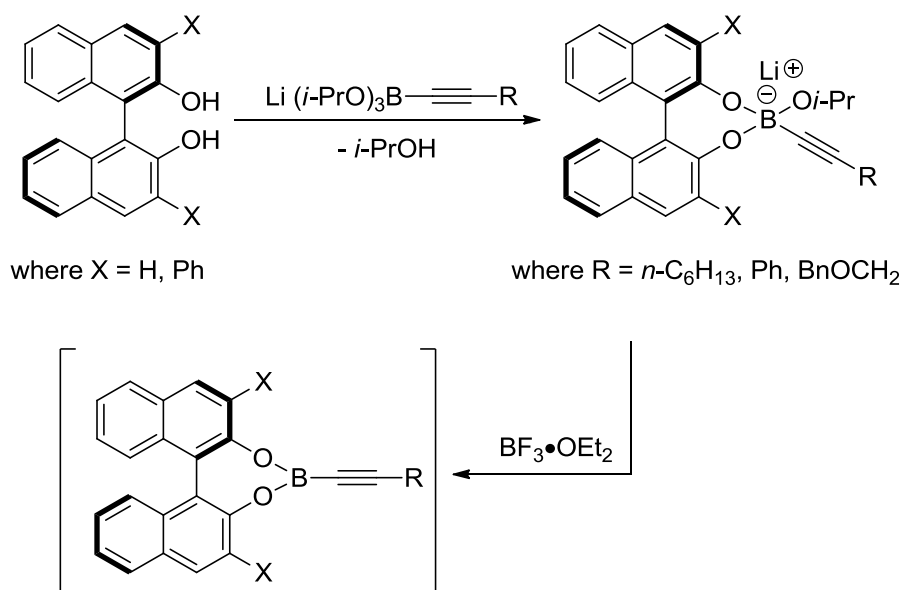
**Table 3.1: Attempted synthesis of dialkyl trifluoromethyl boronates**



Entry	OR Group	X (Counter Ion)	Yield
1	OMe	K	N.D.
2	OMe	Cs	N.D.
2	OEt	K	N.D.
3	OEt	Cs	N.D.
4	O <i>i</i> -Pr	K	N.D.

\* N.D. indicates reaction was unsuccessful, starting material recovered

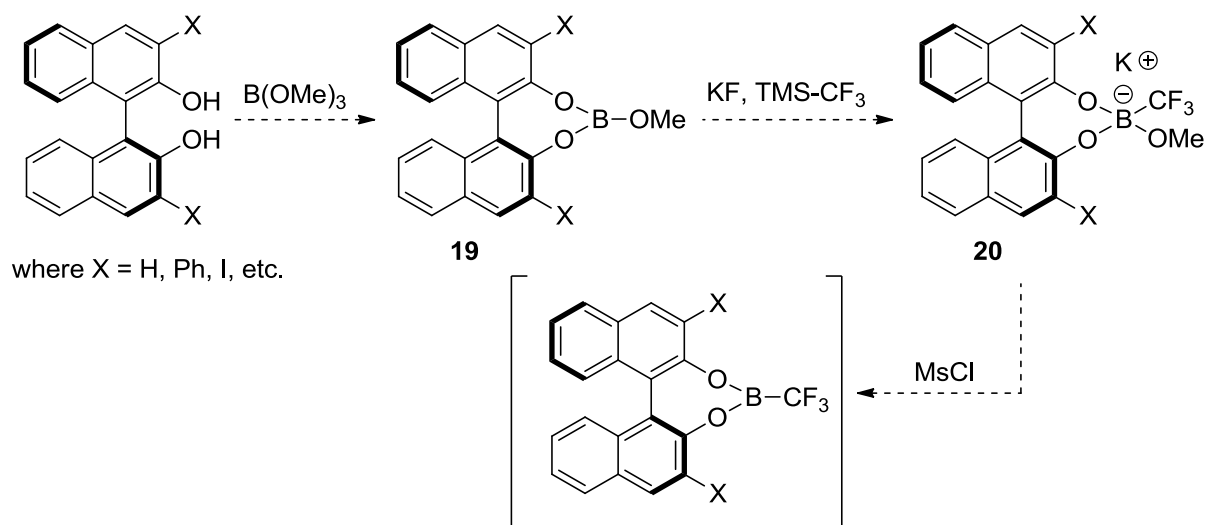
The next idea was to attempt to prepare a binaphthol-trifluoromethyl borate complex for use in the conjugate addition. The inspiration for this work was drawn from the first asymmetric conjugate alkynylation paper by Chong and co-workers published in 2000; the reaction of a 3,3'-disubstituted binaphthol with lithium *B*-1-octynyltriisopropylborate followed by the removal of *i*-PrOH to deliver an alkynyl-binaphthol-borate complex.<sup>98</sup> Subsequent treatment with acid, such as hydrogen chloride or boron trifluoride diethyl etherate (BF<sub>3</sub>·OEt<sub>2</sub>) furnished the reactive trivalent boronate (Scheme 3.7).



**Scheme 3.7: Preparation of binaphthol-modified alkynylboronates**

Although it has been reported in the literature that the reaction of binaphthol with triphenyl borate generates the expected mixed borate, Chong and co-workers were unable to reproduce this result.<sup>99</sup>

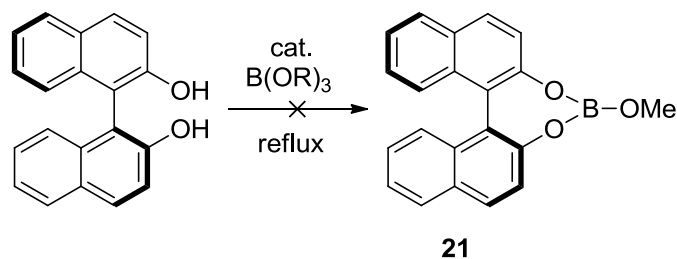
We envisaged that by mixing equimolar amounts of binaphthol with a trialkyl borate, such as trimethyl borate followed by treatment with acid, we would be able to generate a mixed borate species **19** similar to the active reagent in the alkynylation (Scheme 3.8). From this mixed borate, we would then attempt to follow the procedure of Kolomeitsev to prepare the mixed borate salt **20** bearing a trifluoromethyl group, which in turn could be dealkoxylated to generate the active boronate species for use in conjugate additions (Scheme 3.8).



**Scheme 3.8: Planned preparation of a mixed trifluoromethyl-containing binaphthol boronate**

Initial efforts towards this sequence began by refluxing equimolar amounts of trimethyl borate and binaphthol through a Soxhlet extractor filled with 4Å molecular sieves, to remove the methanol and drive the transesterification to completion. This proved to be unsuccessful, as only starting material was recovered. We hypothesized that a catalyst may be necessary to drive the transesterification forward. Subsequent attempts employed the same protocol but with the use of tosic acid (*p*-toluenesulfonic acid) monohydrate as the catalyst (Table 3.2).

**Table 3.2: Attempted preparation of a mixed binaphthol-borate 21**



Entry	Boronate	Catalyst	Catalyst Equiv.	Additive	Solvent	Yield of 21
1	B(OMe) <sub>3</sub>	-	-	4Å MS	CH <sub>2</sub> Cl <sub>2</sub>	N.D.
2	B(OMe) <sub>3</sub>	-	-	4Å MS	CHCl <sub>3</sub>	N.D.
3	B(OMe) <sub>3</sub>	-	-	4Å MS	CH <sub>3</sub> -Ph	N.D.
4	B(OMe) <sub>3</sub>	TsOH·H <sub>2</sub> O	1	4Å MS	CHCl <sub>3</sub>	N.D.
5	B(OMe) <sub>3</sub>	TsOH·H <sub>2</sub> O	1	-	CHCl <sub>3</sub>	N.D.
6	B(OMe) <sub>3</sub>	TsOH·H <sub>2</sub> O	0.1	4Å MS	CHCl <sub>3</sub>	N.D.
7	B(OMe) <sub>3</sub>	CSA	1	4Å MS	CHCl <sub>3</sub>	N.D.
8	B(OMe) <sub>3</sub>	CSA	6	4Å MS	Neat	N.D.
9	B(OPh) <sub>3</sub>	-	-	-	CH <sub>2</sub> Cl <sub>2</sub>	N.D.

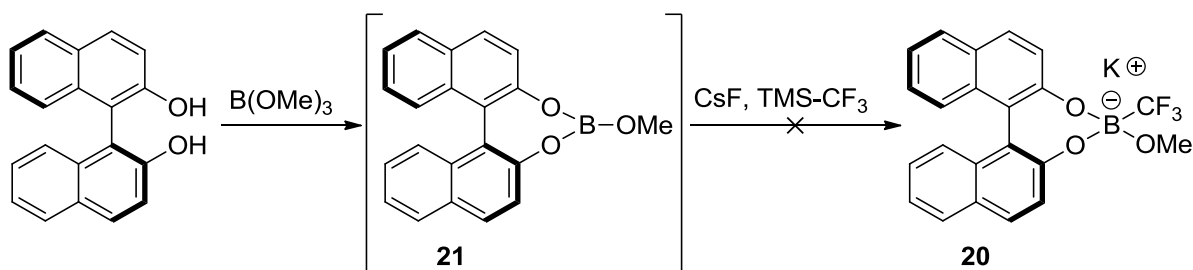
\* N.D. indicates reaction was unsuccessful, starting material recovered

To our surprise, after refluxing the reaction for 3 days, we observed the disappearance of the binaphthol OH peak situated at 5 ppm in the crude <sup>1</sup>H NMR. Carrying this material forward which we believed to be **21**, KF and Me<sub>3</sub>SiCF<sub>3</sub> were added to the mixed boronate in THF, in an attempt to generate the mixed trifluoromethyl-containing binaphthol borate salt. However, this reaction did not proceed, and simply binaphthol starting material was isolated, which suggested that although compound **21** had formed, it decomposed.

Because the monohydrate of tosic acid was used, we presumed that the water present in the reaction mixture led to the hydrolysis of borate **20**. To overcome this, the acid catalyst in the transesterification was changed to anhydrous CSA (camphorsulfonic acid), and the reaction was set-up inside a glove box.

In further investigations, the amount of catalyst was varied. Both catalytic and stoichiometric amounts of either the CSA or tosic acid catalyst were used in the reaction. However, these reactions also proved to be unsuccessful, simply returning unreacted binaphthol. We wondered whether or not water was essential for initiating the transesterification, and thus decided to add an equivalent to the reaction to determine if that would help it proceed. Again, this simply returned un-reacted binaphthol.

It was presumed that perhaps the mixed binaphthol boronate **19** was hydrolyzed during the attempted isolation, or in the work-up procedure. To combat this, we attempted to run a tandem transesterification, followed by trapping of the CF<sub>3</sub> group (Scheme 3.9).



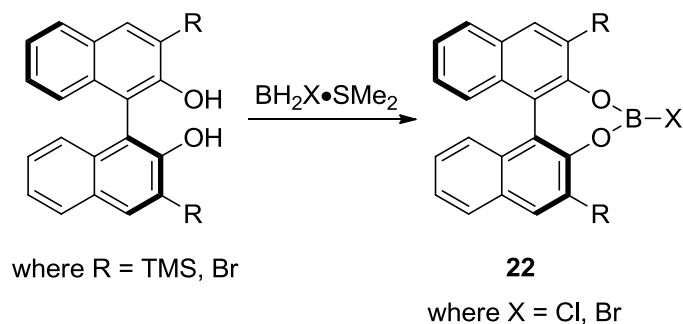
**Scheme 3.9: Modified procedure towards binaphthol-borate species 20**

The nucleophilic source of fluoride for this process was changed from KF to CsF (caesium fluoride), as a more nucleophilic source of F<sup>-</sup> based on the “large counter-ion effect” would perhaps decrease the reaction time. CsF was employed in the reaction sequence depicted in



Scheme 16 and resulted in a vigorously bubbling reaction mixture immediately following the addition. However, the preparation of **20** proved to be unsuccessful, with binaphthol starting material once again recovered. These failures resulted in a shift of focus towards preparing an alternative mixed binaphthol-borate.

Our next idea was inspired by a paper published by Kaufmann *et al.* that reported the synthesis of new mixed binaphthol-boronates for use in stereoselective syntheses.<sup>100</sup> By using a binaphthol with substitution at the 3,3'-position such as a halogen or trimethylsilyl group, the reaction with borane complexes, hydrohaloboranes or boric acid leads to the formation of a seven-membered dioxadihydroborepine system (**22**) to avoid steric strain (Scheme 3.10).<sup>100</sup>

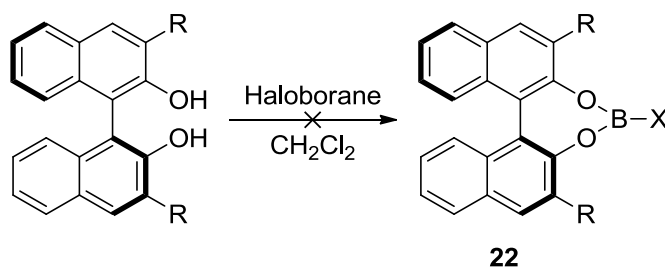


### Scheme 3.10: Formation of a mixed binaphthol-haloboronate

The preparation of the haloborane methyl-sulfide complexes was straight-forward as reported by Brown.<sup>101</sup> Upon addition of the haloborane methyl sulfide complex to 3,3'-diiodobinaphthol, the crude  $^1\text{H}$  NMR revealed that no reaction took place, indicating just starting material remained in the reaction mixture. Interestingly, when water was added to the reaction to check for the reactivity of the chloroborane methyl sulfide complex, there was evolution of a gas, presumed to be  $\text{H}_2$ , indicating that active hydride was still present in the flask. The reaction was repeated with the scrupulous exclusion of moisture and air; however unreacted 3,3'-diiodobinaphthol was still

recovered. Other substituted and un-substituted binaphthols were screened in the same reaction; however, none of the binaphthols used led to the desired mixed boronate **22** (Table 3.3).

**Table 3.3: Preparation of the mixed binaphthol haloboronate**

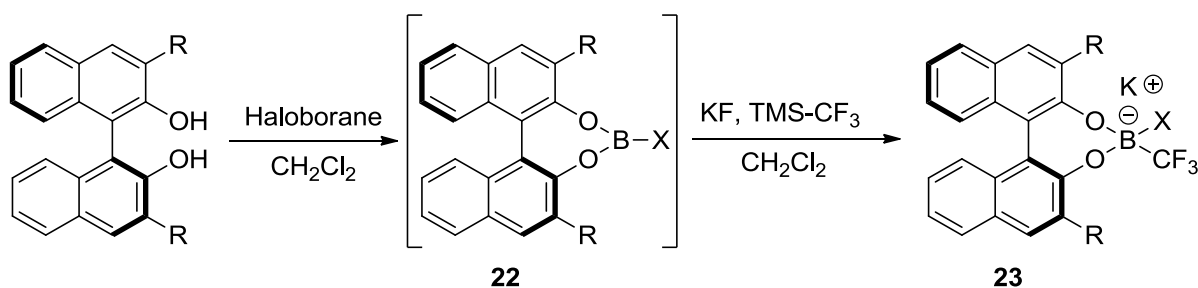


Entry	R	Haloborane Used	Haloborane Equivalents	Yield
1	H	BH <sub>2</sub> Cl·SMe <sub>2</sub>	1	N.D.
2	I	BH <sub>2</sub> Cl·SMe <sub>2</sub>	1	N.D.
3	I	BH <sub>2</sub> Cl·SMe <sub>2</sub>	10	N.D.
4	I	BH <sub>2</sub> Br·SMe <sub>2</sub>	1	N.D.
5	Br	BH <sub>2</sub> Cl·SMe <sub>2</sub>	10	N.D.
6	Br	BH <sub>2</sub> Cl·SMe <sub>2</sub>	1	N.D.
7	Cl	BH <sub>2</sub> Br·SMe <sub>2</sub>	1	N.D.

\* N.D. indicates reaction was unsuccessful, starting material recovered

We concluded that similar to the previous attempts at preparing the binaphthol-boronate **19**, the binaphthol-haloboronate **22** was also hydrolyzed during the isolation. To test this hypothesis, we extracted an aliquot of the reaction mixture with a needle and syringe, and placed the sample in a clean dry flask and left it on the high-vacuum pump to remove volatiles before running the <sup>1</sup>H NMR. To our dismay, the <sup>1</sup>H NMR once again revealed that only unreacted starting material was present in the aliquot.

In desperation, we decided to employ a tandem synthesis, where we would first attempt to make the mixed binaphthol-haloboronate before transferring that mixture to a flask containing both KF and Me<sub>3</sub>SiCF<sub>3</sub>. It was expected that this method would generate the binaphthol-haloboronate complex *in situ*, which would then act as the electrophile for the CF<sub>3</sub> anion which is generated by mixing KF and Me<sub>3</sub>SiCF<sub>3</sub> (Scheme 3.11).



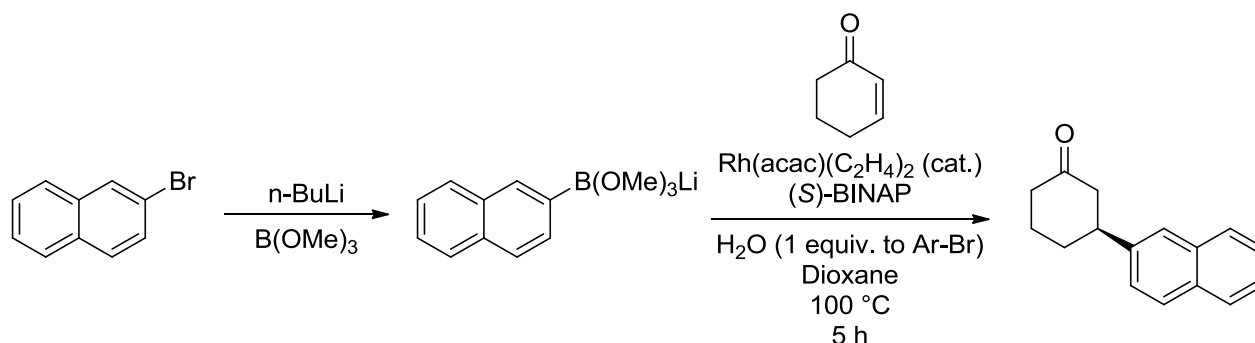
**Scheme 3.11: Preparation of a binaphthol-based trifluoromethyl haloborate 23**

The attempts at preparing compound **23** were unsuccessful after many attempts, and it was deemed that a different approach would be necessary.

### 3.3 Rhodium-Catalyzed Conjugate Additions of Potassium Trifluoromethyl Borates

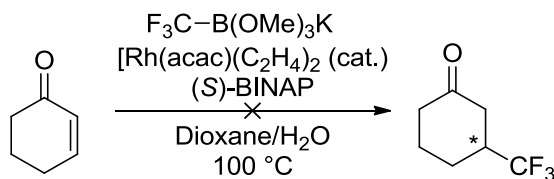
Lithium trimethoxy arylborates have been readily generated *in situ* through a one-pot process by lithiation of an aryl bromide, followed by trapping with trimethyl borate.<sup>102</sup> These reagents have been demonstrated to be excellent nucleophiles in rhodium-catalyzed asymmetric 1,4-additions.<sup>102</sup> The conjugate-additions of these borates have been shown to provide higher yields than reactions employing the analogous arylboronic acid due to eliminating the need to isolate the lithium arylborate.<sup>103</sup>

Careful studies of this reaction have also revealed that the amount of water bears an effect on the yields of the reaction, leaving the enantioselectivity unchanged.<sup>104</sup> A typical example shows the addition of the lithium arylboronate, generated from 2-bromonaphthalene and *n*-BuLi, to cyclohexenone in the presence of 0.1 mol% of the catalyst furnished 3-(2-naphthyl)cyclohexanone in 96% yield and 99% ee (Scheme 3.12).<sup>102</sup>



**Scheme 3.12: Rhodium-catalyzed conjugate additions of lithium trimethoxy arylborates**

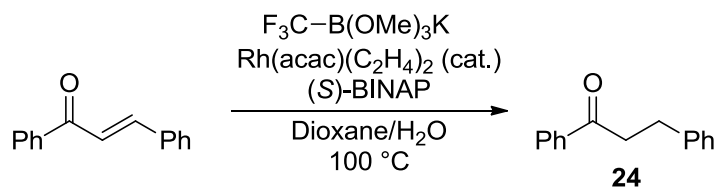
Our initial efforts towards the rhodium-catalyzed 1,4-addition of the trifluoromethyl group utilized the reaction conditions developed by Hayashi for the addition of lithium aryltrimethoxyborates.<sup>102</sup> We screened  $\text{F}_3\text{C-B(OMe)}_3\text{K}$  as the nucleophile, in conjunction with a catalyst complex derived from  $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$  (acetylacetonatobis(ethylene)rhodium(I)) and the chiral phosphine ligand (*S*)-BINAP (Scheme 3.13).



**Scheme 3.13: Rhodium-catalyzed 1,4-addition of potassium trimethoxy trifluoromethylborate**

To our dismay, the reaction did not proceed, and we were returned starting material. The reaction was repeated without any change in fortune. Furthermore, the control experiment was run using the same substrate, but phenylboronic acid as the nucleophile successfully furnished the addition product.

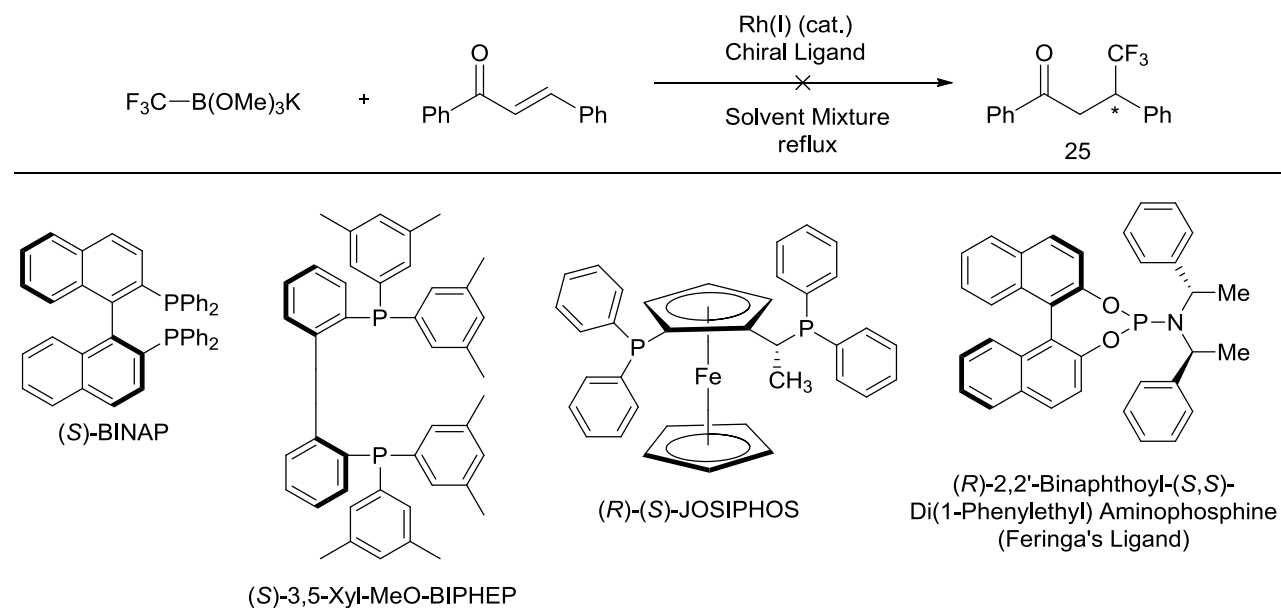
We decided to change the substrate from 2-cyclohexenone to (*E*)-chalcone to see if an acyclic enone would deliver the desired product. When (*E*)-chalcone was subjected to the same reaction conditions, a new product was spotted while following the reaction by TLC. Subsequent work-up of the reaction revealed and analysis of the crude  $^1\text{H}$  NMR revealed this new product to be the reduced enone, 1,3-diphenyl-1-propanone (**24**), and we attributed this product to be the result of a conjugate reduction (Scheme 3.14).



**Scheme 3.14: Conjugate reduction of (*E*)-chalcone**

In an attempt to localize the source of hydride, we set up a similar reaction only this time excluding water from the solvent mixture. The reaction was progressively monitored by  $^1\text{H}$  NMR, but as we were left with un-reacted starting material remaining, it was concluded that without water no reaction took place. Next, another reaction was set-up, but this time the (*S*)-BINAP catalyst was excluded. Frustratingly, we isolated the same conjugate reduction product found when the BINAP catalyst was present in the reaction mixture, thus suggesting that other phosphine-based catalysts should be screened. A summary of the preliminary results are highlighted in Table 3.4.

**Table 3.4: Preliminary results of the Rh-catalyzed 1,4-addition of trifluoromethylborates**



Entry	Rhodium Catalyst	Chiral Ligand	Solvent Mixture	Product
1	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	( <i>S</i> )-BINAP	Dioxane/H <sub>2</sub> O	<b>24</b>
2	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	-	Dioxane/H <sub>2</sub> O	<b>24</b>
3	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	( <i>S</i> )-BINAP	Dioxane	N.R.*
4	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	( <i>S</i> )-BINAP	CF <sub>3</sub> -Ph/H <sub>2</sub> O	<b>24</b>
5	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	( <i>S</i> )-BINAP	DMF	<b>24</b>
6	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	( <i>R</i> )-( <i>S</i> )-JOSIPHOS	Dioxane/H <sub>2</sub> O	<b>24</b>
7	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	( <i>S</i> )-3,5-Xyl-MeO-BIPHEP	Toluene/H <sub>2</sub> O	N.R.*
8	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	Feringa's Ligand	Dioxane/H <sub>2</sub> O	2.5:1 of <b>24</b> to chalcone
9	[Rh(cod) <sub>2</sub> ] <sub>2</sub> BF <sub>4</sub>	( <i>S</i> )-BINAP	Dioxane/H <sub>2</sub> O	<b>24</b>
10	[Rh(OH)(cod)] <sub>2</sub>	( <i>S</i> )-BINAP	Dioxane/H <sub>2</sub> O	<b>24</b>

\* N.R. designates no reaction – recovery of starting material

Interestingly, when the solvent in the reaction was changed to CF<sub>3</sub>-Ph, the conjugate reduction product was still found in the crude NMR, but to a significantly lower extent. The reduction

product only constituted 10% of the crude reaction mixture, with the remainder of the reaction mixture constituting unreacted (*E*)-chalcone (Table 3.4, entry 4).

BINAP had proved to be the only catalyst to deliver any reactivity among the phosphine-based ligands that were screened. In an attempt to deter the formation of the conjugate reduction product, we decided to examine different solvents and their effect on the formation of **24**. The first solvent screen was DMF, as we were interested in the effect of a polar-aprotic solvent on the reaction (Table 3.4, entry 5). However, the conjugate reduction product was again identified in the crude NMR, which indicated the solvent had little effect on the reaction.

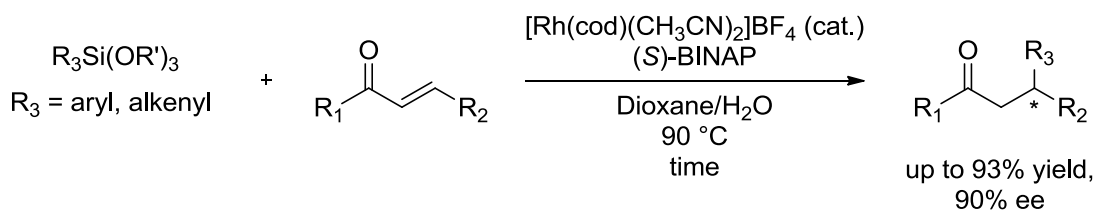
We next screened different chiral phosphine-based ligands, hoping to diminish the formation of the conjugate reduction product. When (*R*)-(*S*)-JOSIPHOS ((2*R*)-1-[(1*R*)-1-(Dicyclohexylphosphino)ethyl]-2-(diphenylphosphino)ferrocene) was used, the conjugate reduction product was found in the crude <sup>1</sup>H NMR, and constituted approximately 10% of the reaction mixture (Table 3.4, entry 6). The next experiment employed (*S*)-3,5-Xyl-MeO-BIPHEP ((*S*)-(-)-2,2'-Bis[di(3,5-xyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl) as the ligand and toluene/water as the solvent mixture (Table 3.4, entry 7). Under these conditions, the reaction failed to proceed. When Feringa's phosphoramidite ligand was used, a 2.5:1 mixture of conjugate reduction product to starting material was found present in the crude NMR (Table 3.4, entry 8). It seemed that the conjugate reduction product was forming regardless of the ligand, albeit in different amounts depending on which ligand was used.

The final variable to be examined was the source of rhodium (I) in the reaction mixture. A cationic source of rhodium (Table 3.4, entry 8) was screened in identical conditions, but nevertheless once again led to the conjugate reduction product **24** in the crude NMR.

$[\text{Rh}(\text{OH})(\text{cod})]_2$  (Hydroxy(cyclooctadiene)rhodium(I) dimer) was also screened, as Hayashi reported this catalyst to be more reactive than the neutral  $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ . Hayashi found that by using  $[\text{Rh}(\text{OH})(\text{cod})]_2$ , the conjugate additions could be run at lower temperatures, thus leading to higher enantiomeric ratios due to a further difference in free energy between diastereomeric transition states.<sup>104</sup> Additionally, the yields are reportedly higher due to the suppressing the hydrolysis of boronic acids, the main side reaction.<sup>104</sup> However, we found the use of  $[\text{Rh}(\text{OH})(\text{cod})]_2$  unfortunately led to the formation of product **24**.

### 3.4 Rhodium-Catalyzed Conjugate Additions of Organosilanes

With the addition of potassium organotrifluoroborates appearing desolate, we next investigated the rhodium-catalyzed addition of organosilicon reagents. Inoue reported the asymmetric 1,4-addition of aryl- and alkenyltrialkoxysilanes to  $\alpha,\beta$ -unsaturated ketones in the presence of 2 mol % of a cationic rhodium complex generated by mixing  $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$  and (*S*)-BINAP (Scheme 3.15).<sup>105</sup>



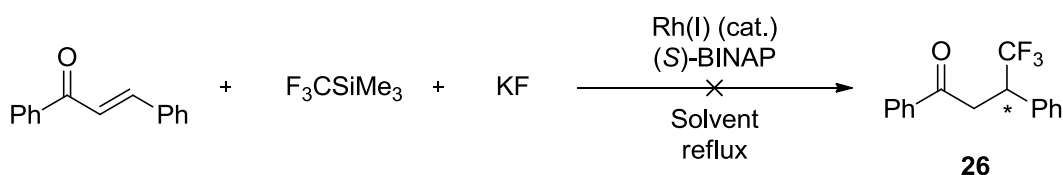
**Scheme 3.15: Rh-catalyzed conjugate addition of organosilanes**

In these reactions the use of 1.5 equivalents of the BINAP ligand were essential to furnishing adducts in high enantioselectivity due to the fact that the rhodium catalyst is more active on its own than in a complex with BINAP.<sup>105</sup> Substrates that can be added include aryl-, vinyl- and styrenyl-trialkoxysilanes all in good yields and high enantioselectivities.<sup>105</sup>



Since it had been shown that siloxanes were capable of transmetallating with rhodium species, we postulated that perhaps we would be able to generate the silicate by mixing Ruppert's reagent with a nucleophilic source of fluoride, which would then hopefully transmetallate with rhodium and undergo a 1,4-addition with an  $\alpha,\beta$ -unsaturated ketone (Table 3.5).

**Table 3.5: Rh-catalyzed conjugate additions of silicates generated from Ruppert's reagent**



Entry	Rhodium Catalyst	Solvent	Temperature	Yield of 26
1	[Rh(cod) <sub>2</sub> ] <sub>2</sub> BF <sub>4</sub>	Dioxane/H <sub>2</sub> O	100 °C	N.R. <sup>*</sup>
2 <sup>a</sup>	[Rh(cod) <sub>2</sub> ] <sub>2</sub> BF <sub>4</sub>	Dioxane/H <sub>2</sub> O	100 °C	N.R. <sup>*</sup>
3	[Rh(cod) <sub>2</sub> ] <sub>2</sub> BF <sub>4</sub>	Dioxane/H <sub>2</sub> O	rt	N.R. <sup>*</sup>
4 <sup>b</sup>	[Rh(cod) <sub>2</sub> ] <sub>2</sub> BF <sub>4</sub>	THF	rt	N.R. <sup>*</sup>

<sup>a</sup> Reaction run without KF, <sup>b</sup> Reaction run without (S)-BINAP

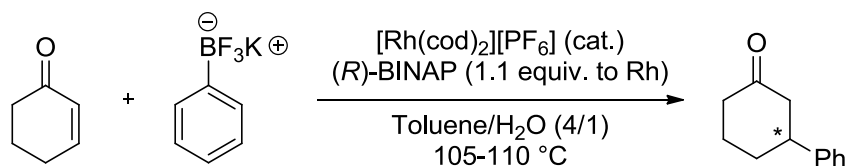
\* N.R. designates no reaction

Based on the results from our brief screen, we decided to turn our focus to finding another class of nucleophiles that we could develop from Ruppert's reagent to successfully undergo rhodium-catalyzed conjugate additions.

### 3.5 Rhodium-Catalyzed Conjugate Additions of Potassium Trifluoromethyl Trifluoroborates

Potassium organotrifluoroborates are another class of borate and are generally more stable than the corresponding boronic acid derivative.<sup>104</sup> Additionally, these borates have been shown to be efficient nucleophiles in rhodium-catalyzed conjugate additions.<sup>106</sup> In a representative example,

when potassium phenyltrifluoroborate is reacted with 2-cyclohexenone in a refluxing toluene/H<sub>2</sub>O solvent mixture, the addition product is obtained in 99% yield and 98% ee (Scheme 3.16).<sup>106</sup>



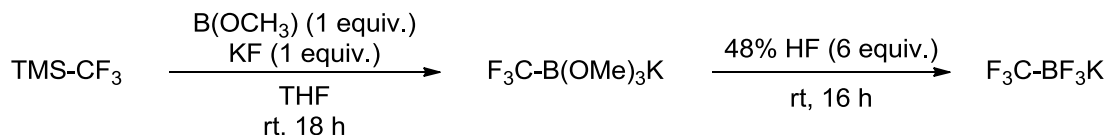
**Scheme 3.16: Rhodium-catalyzed conjugate addition of phenyltrifluoroborate**

The catalyst employed in these reactions is a cationic source of rhodium (I), compared to the neutral rhodium catalysts employed in the reactions of arylboronic acids and lithium trimethoxy arylborates.<sup>106</sup> Neutral rhodium catalysts have been found to work poorly in the conjugate additions of trifluoroborates.<sup>106</sup> Additionally, it has been documented that the enantioselectivity is highly dependent on the reaction media; a mixed solvent system composed of toluene as the organic constituent combined with an excess of water is crucial to obtain high selectivities.<sup>106</sup>

In terms of the scope of nucleophiles added, vinyltrifluoroborates were found to successfully undergo conjugate additions in this system.<sup>106</sup> This was the first reported addition of this functional group in rhodium-catalyzed 1,4-addition, as a result of the instability of the analogous vinylboronic acid.<sup>106</sup> In addition to the BINAP ligand, other chiral bisphosphine ligands such as (*R*)-(*S*)-Josiphos and (*R*)-MeO-BIPHEP have been found to confer high enantioselectivities.<sup>106</sup>

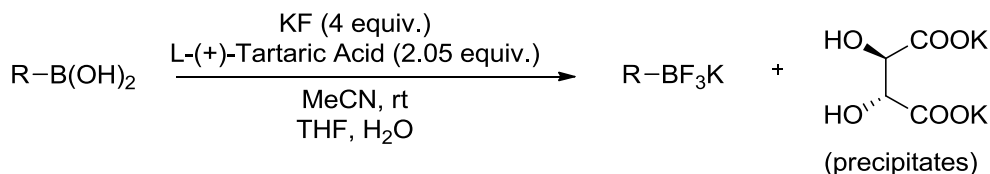
In 2003, Molander and Hoag published an improved synthesis of potassium trifluoromethyltrifluoroborate [K(CF<sub>3</sub>BF<sub>3</sub>)].<sup>107</sup> Their method began by treating Ruppert's reagent with trimethyl borate in the presence of KF, identical to the paper published by Kolomeitsev *et*

*al.*<sup>107</sup> From the borate salt produced in the first step, aqueous hydrogen fluoride was added and the title compound was isolated in 85% yield (Scheme 3.17).



**Scheme 3.17: Improved synthesis of potassium trifluoromethyl trifluoroborate**

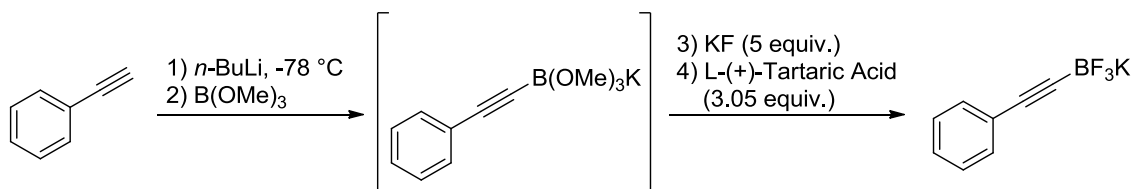
In 2012, Lloyd-Jones *et al.* developed an alternative preparation for a variety of organotrifluoroborate salts in non-etching conditions.<sup>108</sup> This method eliminated the use of HF thus improving the overall safety of the procedure, and eliminated the etching of glassware caused by KF (Scheme 3.18).<sup>108</sup>



**Scheme 3.18: Preparation of organotrifluoroborates under non-HF conditions**

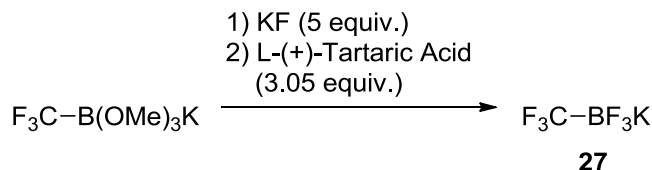
Additionally, the method removed the need for a complicated separation of the product from a mixture of salts due to the low solubility of the bitartrate salt in most organic solvents.<sup>108</sup> By using a stoichiometric amount of L-(+)-tartaric acid, added as a solution in THF, the precipitation of the bitartrate salt drives the conversion of the boronic acid to the trifluoroborate salt.<sup>108</sup>

Lloyd-Jones and co-workers also reported the synthesis of potassium phenylethynyltrifluoroborate in a one pot procedure starting from phenylacetylene. This protocol was most relevant to our work, as the initial steps paralleled the procedure used to prepare the potassium trifluoromethylborate developed by Kolomeitsev (Scheme 3.19).



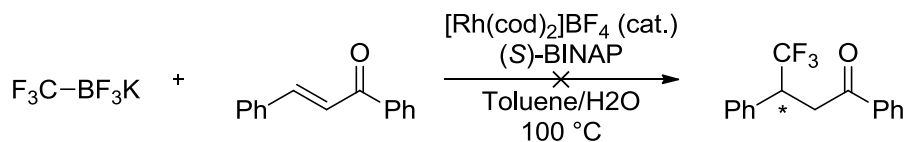
**Scheme 3.19: Synthesis of phenylethynyltrifluoroborate from phenylacetylene**

Beginning with the potassium trimethoxytrifluoroborate salt **14**, we applied the Lloyd-Jones procedure to successfully obtain the corresponding potassium trifluoromethyl trifluoroborate (Scheme 3.20).



**Scheme 3.20: Preparation of potassium trifluoromethyl trifluoroborate**

With trifluoroborate **27** in hand, we next followed the procedure for rhodium-catalyzed additions of potassium trifluoroborates developed by Darses *et al.* (Scheme 3.21).<sup>106</sup>



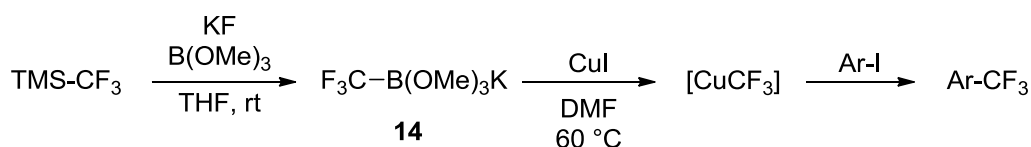
**Scheme 3.21: Rh-catalyzed conjugate additions of potassium trifluoromethyl trifluoroborate**

Once again, we recovered only starting material from the reaction, despite repeated attempts. We decided to depart from rhodium-catalyzed conjugate additions and develop an alternative method to successfully achieve the 1,4-addition of the trifluoromethyl group.

### 3.6 Copper-Catalyzed Conjugate Addition of the Trifluoromethyl Group

The asymmetric copper-catalyzed 1,4-addition of organometallic reagents has been extensively reviewed.<sup>109</sup> When combined with various chiral ligands such as phosphine or phosphoramidite-based ligands, the reactions have been demonstrated to generate materials of high enantiopurity.<sup>109</sup>

In 2011, Gooßen and co-workers published a report detailing the preparation of a  $[\text{CuCF}_3]$  species from potassium trifluoromethyl trimethoxyborate **14** which could carry out the trifluoromethylation of aryl iodides (Scheme 3.22).<sup>110</sup>



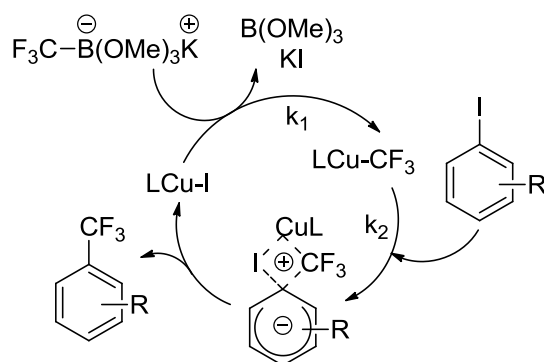
**Scheme 3.22: Copper catalyzed trifluoromethylation of aryl iodides**

To examine the nucleophilicity of the borate salt, the group mixed equimolar amounts of the trifluoromethyl trimethoxyborate salt **14** with CuI in DMF at room temperature and analyzed the resulting suspension by  $^{19}\text{F}$  NMR.<sup>110</sup> A new signal appeared at -28.14 ppm, indicating the presence of an anionic  $[\text{CF}_3\text{CuI}]^-$  species, which confirmed that in the absence of an added base, the borate was able to transfer its  $\text{CF}_3$  group to the copper.<sup>110</sup> Subsequent treatment of 4-iodoanisole with two equivalents of the potassium trifluoromethyl trimethoxyborate salt **14** in the presence of stoichiometric quantities of CuI led to the formation of 4-trifluoromethylanisole in good yield.<sup>110</sup> Additionally, without the addition of a copper (I) source, no reaction took place.

Amii and co-workers published a report which demonstrated that the reaction rate for the Cu-mediated trifluoromethylation may be improved by the addition of chelating nitrogen ligands,

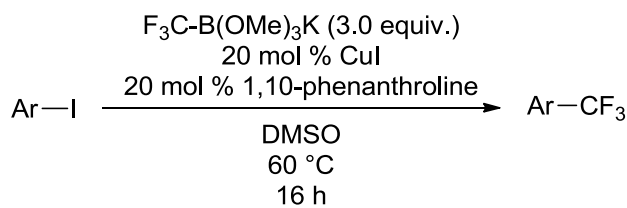
which eventually led to the first copper-catalyzed trifluoromethylation based on Ruppert's reagent.<sup>111</sup> A key observation made in this work however was the rate of the copper-mediated iodide- $\text{CF}_3$  exchange ( $k_1$  in Scheme 3.23) is quite often much lower than that of the  $\text{CF}_3$  group transfer from the trifluoromethylating reagent (in this case, Ruppert's reagent) to the copper ( $k_2$  in Scheme 3.23).<sup>111</sup> This creates a problem because there is not enough copper iodide reproduced to take up another  $\text{CF}_3$  before the  $\text{CF}_3$  decomposes.<sup>111</sup> By increasing the nucleophilicity of the  $[\text{CuCF}_3]$  species by using electron-donating ligands for example, the group were able to achieve a higher rate of catalytic turnover.<sup>111</sup>

Inspired by this, Gooßen and co-workers set out to develop a catalytic version of this reaction, and evaluated the use of trifluoromethyl borate salts in the reaction with a nitrogen-based ligand-stabilized copper halide complex,  $\text{LCu-I}$ , formed by mixing equimolar amounts of copper (I) iodide with 1,10-phenanthroline.<sup>110</sup> They proposed a mechanism for this process highlighted below (Scheme 3.23).



**Scheme 3.23: Catalytic cycle for the copper-catalyzed trifluoromethylation**

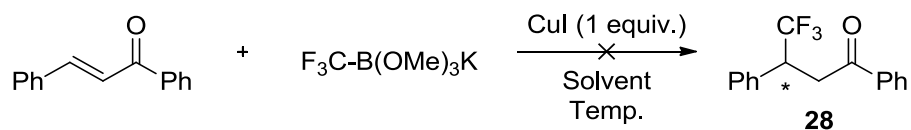
The group found that the optimal solvent for the process was DMSO. As a result of their efforts, they had pioneered an efficient method for the trifluoromethylation of both electron rich and deficient arenes and heteroarenes (Scheme 3.24).



**Scheme 3.24: Cu-catalyzed trifluoromethylation of arenes and heteroarenes**

Inspired by these reports, we attempted to prepare the  $[\text{CuCF}_3]$  species and examine its reactivity as a nucleophile for the conjugate addition to chalcone (Table 3.6).

**Table 3.6: Attempted Cu-catalyzed conjugate addition of  $\text{CF}_3$**



Entry	Solvent	Temperature	Yield of <b>28</b>
1	DME	rt	N.R. <sup>*</sup>
2	Toluene	rt	N.R. <sup>*</sup>
3	$\text{CH}_2\text{Cl}_2$	rt	N.R. <sup>*</sup>

<sup>\*</sup> N.R. designates no reaction – isolated starting material

<sup>a</sup> Reaction was run in the presence of Feringa's catalyst (33 mol %)

DME was chosen as the reaction solvent as it had been shown to be effective in the copper-catalyzed conjugate addition of dialkylzinc reagents.<sup>109</sup> After no reactivity was observed in DME, toluene and  $\text{CH}_2\text{Cl}_2$  were screened (Table 3.6, entry 2 and 3 respectively; however, no reactivity was observed in either of these solvents).

We suspected that the lack of reactivity was because the  $[\text{CuCF}_3]$  species was not forming in the reaction mixture. To investigate this, equimolar amounts of potassium trifluoromethyl

trimethoxyborate **14** and copper (I) iodide were combined in DME at room temperature. After 3 hours, the crude  $^{19}\text{F}$  NMR revealed a small peak at -28 ppm composing approximately 10% of the reaction mixture that was identified as the  $[\text{CuCF}_3]$  species. The remaining percentage of the reaction mixture consisted of Ruppert's reagent. This result had indicated that we were able to reproduce the work of Gooßen and co-workers and did prepare the  $[\text{CuCF}_3]$  species; however, it did not undergo the conjugate addition reaction with chalcone.

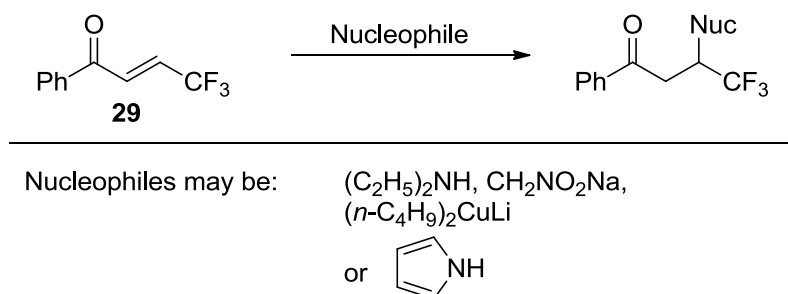
As a result of these failed attempts at generating a reagent to add the  $\text{CF}_3$  group to an  $\alpha,\beta$ -unsaturated ketone, we decided that the best chance we would have at successfully generating  $\beta$ -trifluoromethylated compounds would have to come from a different approach. The next chapter examines the literature precedent for the conjugate additions to various  $\beta$ -trifluoromethyl- $\alpha,\beta$ -unsaturated enones and marks our attempts at applying the chemistry developed in our lab towards the asymmetric synthesis of  $\beta$ -trifluoromethylated compounds.



## Chapter 4: Development of Asymmetric Conjugate Additions to $\beta$ -Trifluoromethyl $\alpha,\beta$ -Unsaturated Enones

### 4.1 Reported Conjugate Additions to $\beta$ -Trifluoromethyl $\alpha,\beta$ -Unsaturated Enones

Ogoshi published one of the first reports detailing the functionalization of a  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketone in 1985 (Scheme 4.1).<sup>112</sup> Though the scope of the reaction was quite limited, this publication highlighted  $\beta$ -trifluoromethyl enones as useful synthetic building blocks in the preparation of trifluoromethylated compounds.<sup>112</sup>



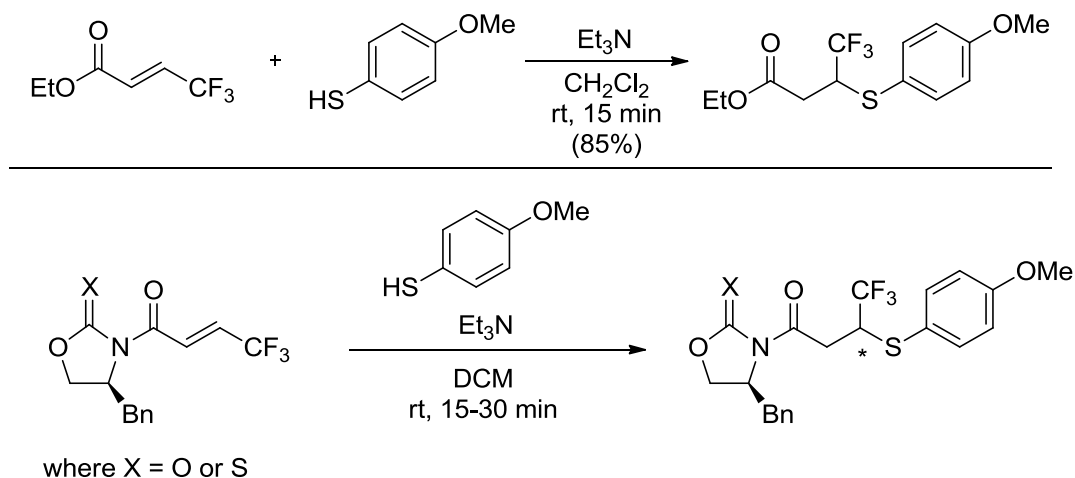
**Scheme 4.1: 1,4-addition of various nucleophiles to 29**

Further development on the functionalization of these substrates came from Contreras and co-workers who employed the conjugate addition of KCN to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketones as the first step in a pathway towards the synthesis of aminopyridazines bearing a trifluoromethyl moiety.<sup>113</sup>

Yamazaki, Kitazume and co-workers found  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated esters to be efficient Michael acceptors in the diastereoselective conjugate additions of lithium enolates, expanding the scope of reported  $\beta$ -trifluoromethyl enone substrates for 1,4-additions.<sup>114</sup> The group has since extended the scope of nucleophiles to include lithium enolates derived from chiral acyloxazolidinones in subsequent transformations.<sup>114,115</sup> They also reported the addition of

organomagnesium and organolithium species in the presence of copper (I) species towards chiral oxazolidinone-based  $\beta$ -trifluoromethyl enones.<sup>116</sup> Inspired by these initial studies, further reports emerged detailing the use of lithium enolates derived from various ketones, esters or amides as nucleophiles in Michael additions.<sup>114,117,118</sup>

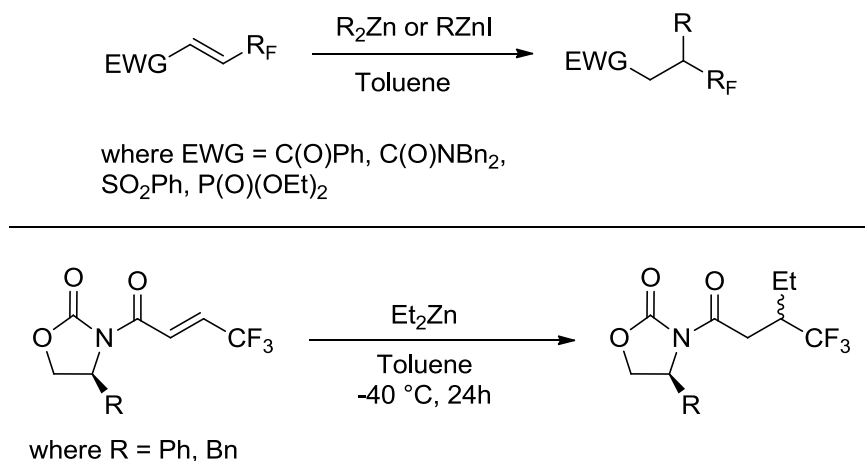
These initial studies were the inspiration for further groups such as Gestmann and co-workers to examine the addition of the Schiff base of *N*-(diphenylmethylene) glycinate to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated esters as a key step in the synthesis of the pure enantiomers of pyroglutamic esters.<sup>119</sup> Similarly, Sani *et al.* have detailed the novel synthesis of an inhibitor of matrix metalloproteinases via the conjugate addition of *p*-methoxythiophenol to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated esters.<sup>120</sup> The group expanded their methodology to include the diastereoselective addition of *p*-methoxythiophenol to chiral enones based on Evans's chiral oxazolidinones (Scheme 4.2).<sup>120</sup>



**Scheme 4.2: Conjugate addition of *p*-methoxythiophenol to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated esters and *N*-acyloxazolidinones**

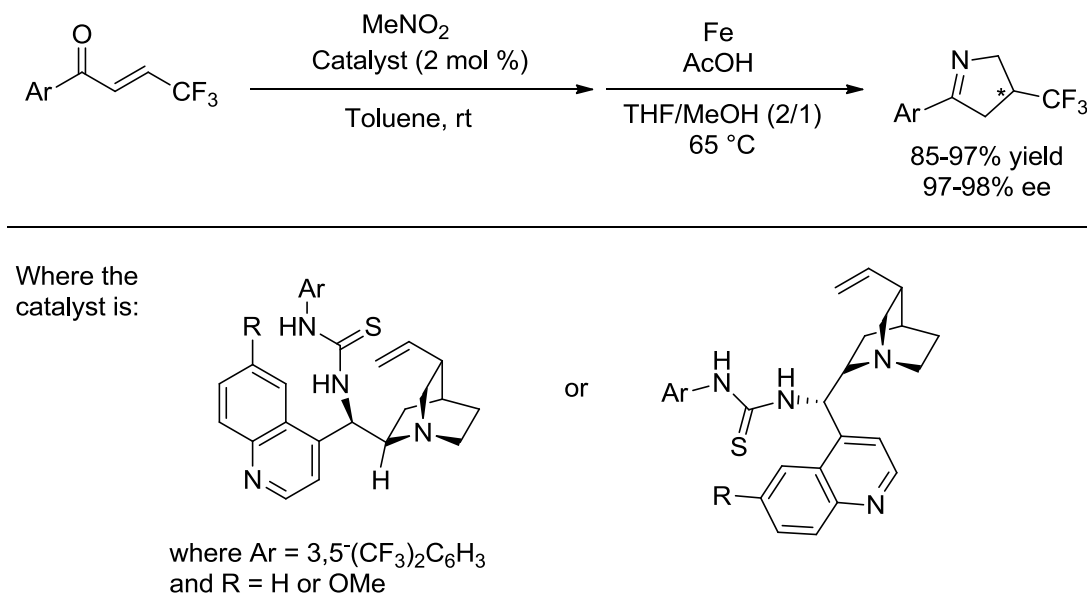
Furthermore, the highly diastereoselective conjugate additions of various lithium enolates to  $\alpha,\beta$ -unsaturated sulfoxides have been reported by Yamazaki and Ishikawa *et al.*, and were applied towards the synthesis of biologically relevant therapeutics.<sup>121</sup> Building upon this initial discovery, the group developed a highly stereoselective asymmetric Michael addition by employing a chiral  $\alpha,\beta$ -unsaturated sulfoxide as the Michael acceptor in lithium enolate additions.<sup>122</sup> Similar to this work, Kitazume and Yamazaki and co-workers detailed two methods for the synthesis of  $\alpha$ -trifluoromethylated aldehydes which employed the addition of a lithium enolate to a chiral sulfoxide.<sup>123</sup>

More recently, Konno and co-workers expanded the scope of nucleophiles, reporting the first racemic 1,4-addition of organozinc reagents to a range of  $\beta$ -fluoroalkylated substrates without the use of transition metals or Lewis acids.<sup>124</sup> The group was able to add various alkyl and dialkylzinc reagents to a multitude of  $\beta$ -trifluoromethyl enones.<sup>124</sup> The group also highlighted preliminary efforts towards a diastereoselective 1,4-conjugate addition to  $\beta$ -trifluoromethyl chiral enones derived from Evans's chiral oxazolidinones (Scheme 4.3).<sup>124</sup>



**Scheme 4.3: Addition of organozinc reagents to  $\beta$ -trifluoromethyl substrates**

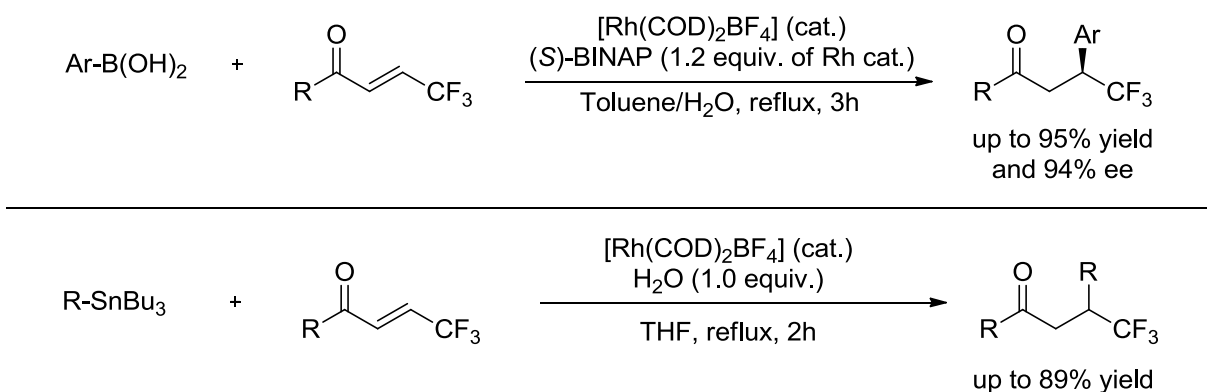
Despite the numerous reported efforts of racemic conjugate additions, very few reports have emerged regarding the asymmetric 1,4-addition of nucleophiles to  $\beta$ -fluoroalkylated enones. Notably, Shibata and co-workers have developed a catalytic enantioselective synthesis of  $\beta$ -trifluoromethyl pyrrolines via the organocatalyzed-conjugate addition of nitromethane to  $\beta$ -trifluoromethylated enones, followed by a nitro-reduction/cyclization/dehydration sequence (Scheme 4.4).<sup>125</sup>



#### Scheme 4.4: Catalytic enantioselective synthesis of $\beta$ -trifluoromethyl pyrrolines

The use of cinchona alkaloid-thiourea derivatives was found to be very effective in the transformation obtaining both enantiomers in high yields and excellent enantiomeric excess.<sup>125</sup> By using pseudoenantiomeric thiourea derivatives as the catalysts, the opposite stereochemistry was generated in excellent selectivity.<sup>125</sup> This is one of few reported methods to date towards the synthesis of compounds bearing a trifluoromethyl group on a stereogenic carbon.

More relevant to the methods developed in our lab, Konno and co-workers highlighted the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketones in the presence of BINAP in both high yields and enantioselectivities.<sup>126</sup> The initial success of this methodology led to the development of the racemic conjugate additions of arylstannanes to similar parent substrates (Scheme 4.5).<sup>127</sup>



**Scheme 4.5: Rhodium-catalyzed 1,4-additions to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketones**

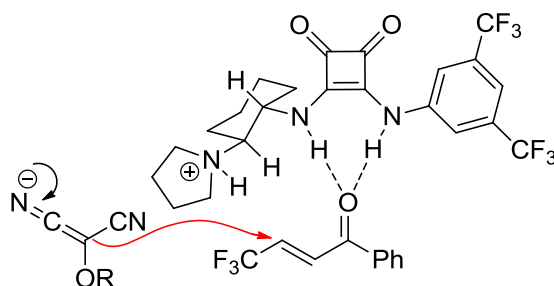
The additions of arylboronic acids to other substrates such as  $\alpha,\beta$ -unsaturated amides, vinyl phosphates and vinyl sulfones were examined; however, the phosphate and sulfone-based substrates were found to be unreactive under these conditions.<sup>126</sup> By employing organostannanes as the nucleophile in similar reaction conditions, the group were able to successfully obtain adducts derived from vinyl phosphates and vinyl sulfones in higher yields.<sup>126</sup>

At the start of 2013, Lu and co-workers reported the enantioselective conjugate addition of nitroalkanes and other nucleophiles to  $\beta$ -trifluoromethyl acrylamides, catalyzed by Cinchona-alkaloid-thiourea and Takemoto's catalysts. The developed methodology was applied to the synthesis of optically active trifluoromethylated  $\gamma$ -aminobutyric acid in high yields with enantioselectivities of up to 96% (Scheme 4.6).<sup>128</sup>



These adducts can then be unmasked to furnish  $\gamma$ -keto-carboxylic acids, esters and amides in excellent yields and enantioselectivities.<sup>129</sup> The observed asymmetric induction in these reactions is consistent with a pre-transition state assembly wherein the ammonium salt of the catalyst directs the nucleophilic addition of the masked acyl cyanide to the enone, which was activated through hydrogen bonding to both nitrogen atoms of the catalyst (Figure 4.1).<sup>129</sup>

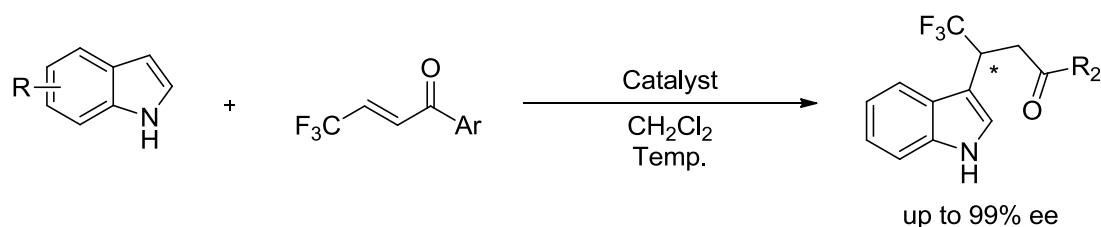
**Figure 4.1: Model for asymmetric induction observed in additions of masked acyl cyanides**



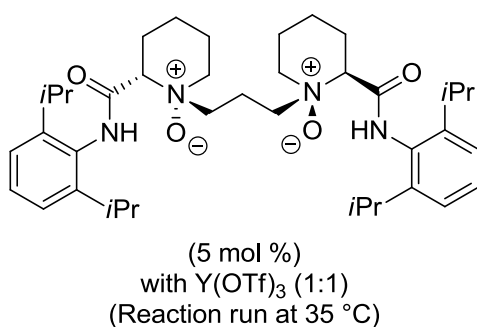
Aside from these few examples of asymmetric conjugate additions to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated enones, several groups have reported the racemic conjugate additions of various nucleophiles to similar substrates. For example, the conjugate additions of acetamides to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketones has played an important role towards the synthesis of various pyrido[2,3]pyrimidin-4(3*H*)-one derivatives, compounds that play an important role in biologically active pharmaceuticals.<sup>130</sup>

Other medicinally relevant trifluoromethylated compounds have arisen from the racemic 1,4-addition to  $\beta$ -keto esters, 1,2-diamines, trialkoxyphosphates, salicylaldehydes, *N*-Tosyl-amines, and enamines.<sup>131-136</sup> Similarly, Langlois *et al.* employed electron rich O- and N-containing heterocycles such as furans, benzofurans, pyrroles, indoles and hydroxycumarins as the nucleophiles in racemic Lewis acid catalyzed 1,4-additions to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated enones.<sup>137</sup>

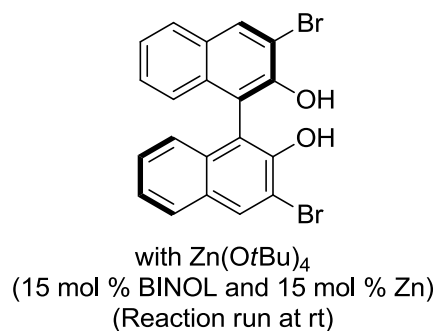
To compensate with the limited examples of asymmetric 1,4-additions to  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated enones, various groups have developed other methods to generate chiral tertiary centers bearing a trifluoromethyl group. The Friedel-Crafts alkylation of indoles with the use of a chiral complex has been reported in literature, though the scope of the reaction is quite limited (Scheme 4.8).<sup>138,139</sup>



Where catalyst represents either:



or

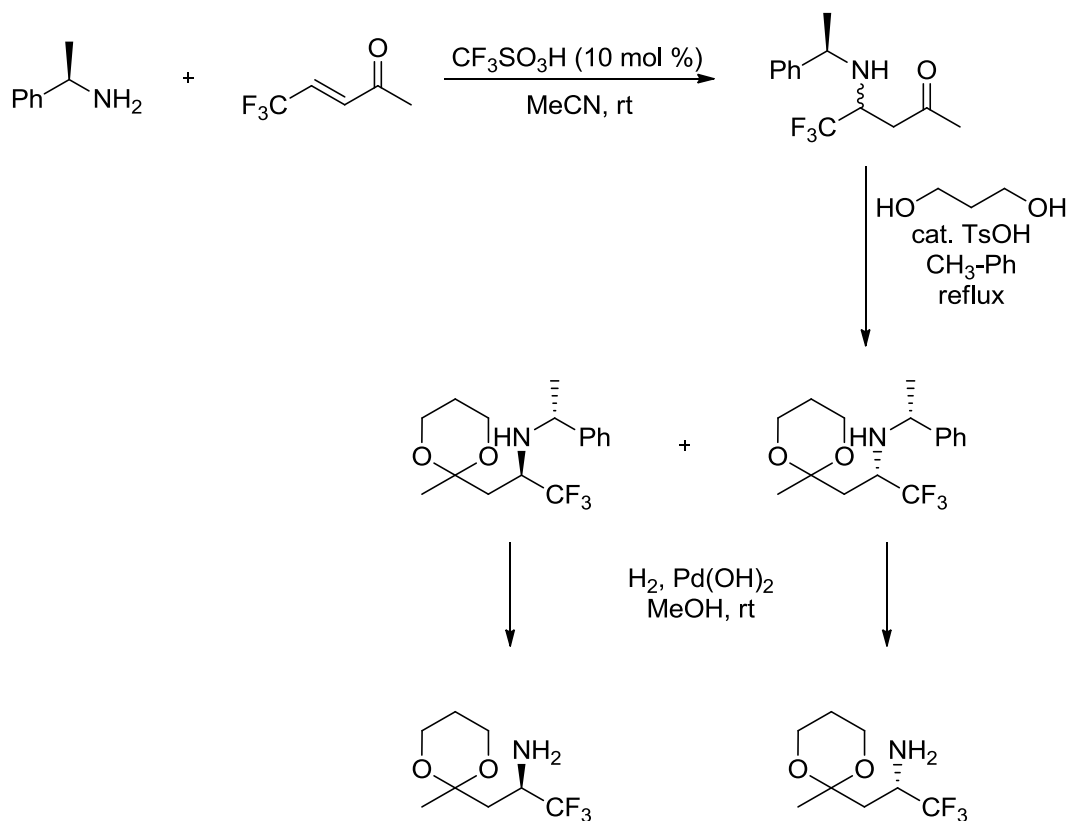


**Scheme 4.8: Enantioselective Friedel-Crafts Alkylation of Indoles with  $\beta$ -trifluoromethyl enone**

With indoles, the enantioselectivity of the reaction was as high as 99% ee.<sup>138</sup> When other nucleophiles such as pyrrole were screened with the same substrates, the enantioselectivities were found to be significantly lower, with the addition product obtained in 55% ee.<sup>138,139</sup>



Aside from the Friedel-Crafts chemistry, enantioenriched trifluoromethyl piperidines have been synthesized through a conjugate addition of a primary amine as reported by Canet *et al* (Scheme 4.9).<sup>140</sup>

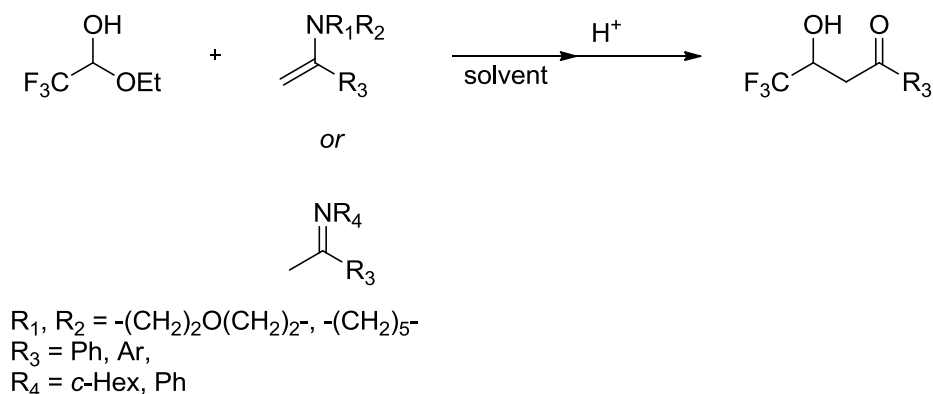


**Scheme 4.9: Conjugate additions of amines with trifluoromethyl enones**

Expanding on this methodology, the group was able to accomplish the diastereoselective synthesis of various trifluoromethyl-substituted piperidine alkaloids.<sup>141</sup> Additionally, trifluoromethyl-piperidine-based  $\gamma$ -amino acids and indolizidines, a class of compounds with increased lipophilicity with potential use as therapeutics to inhibit neurotransmitters in the CNS for treatment of neurological or psychiatric disorders were also prepared.<sup>142</sup>

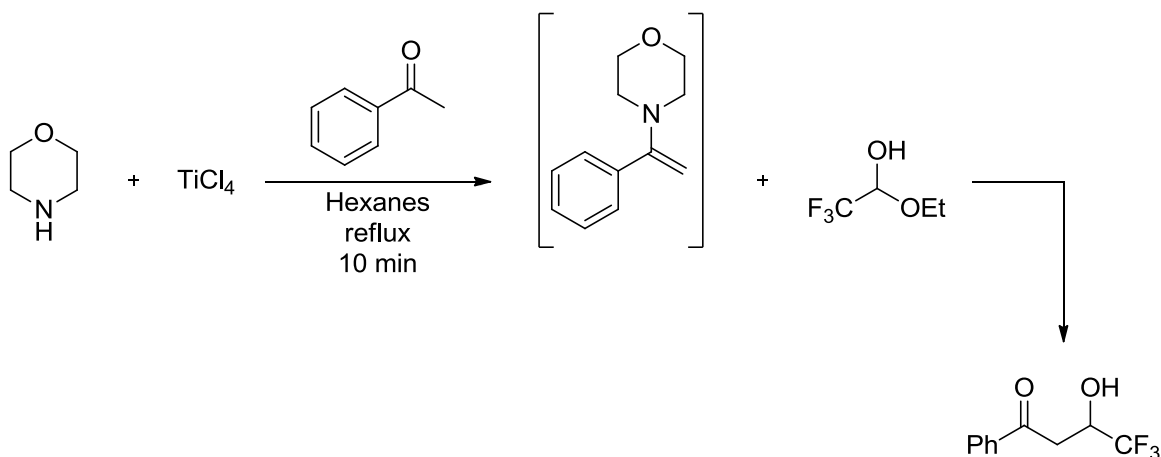
## 4.2 Preparation of the $\beta$ -Trifluoromethyl $\alpha,\beta$ -Unsaturated Ketone Substrates

In 2002, Funabiki, Matsui and co-workers reported the reaction of trifluoroacetaldehyde ethyl hemiacetal with an equimolar amount of an enamine or imine to furnish the corresponding  $\beta$ -hydroxy- $\beta$ -trifluoromethyl ketones in good yields (Scheme 4.10).<sup>143</sup>



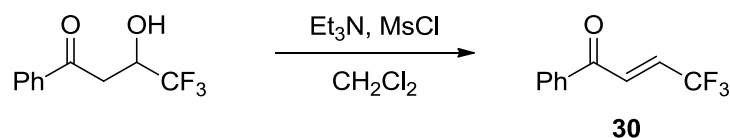
**Scheme 4.10: Preparation of  $\beta$ -hydroxy- $\beta$ -trifluoromethyl ketones from enamines and imines**

The enamines and imines used in this reaction were prepared by mixing the appropriate ketone with morpholine at room temperature in hexane for 1 hour.<sup>143</sup> Our attempts to prepare the enamines in this fashion were unsuccessful. Therefore, we turned to a procedure developed by Carlson and Nilsson, where the enamine was prepared by adding various carbonyl compounds to a preformed titanium tetrachloride-amine complex (Scheme 4.11).<sup>144</sup>



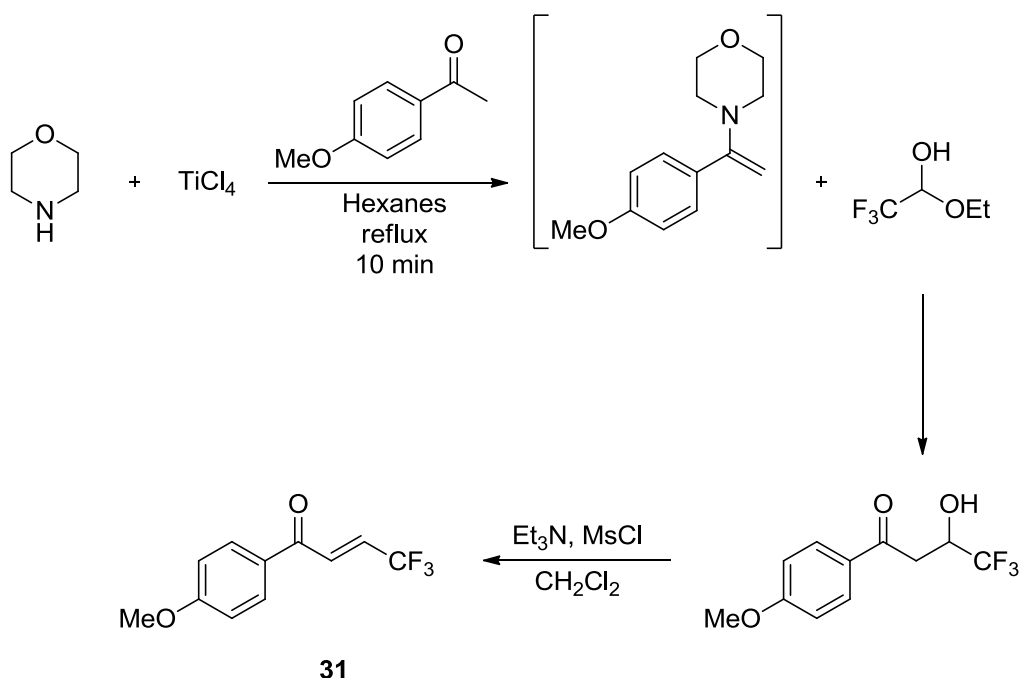
**Scheme 4.11: Modified procedure for the synthesis of  $\beta$ -hydroxy- $\beta$ -trifluoromethyl ketones**

From the  $\beta$ -hydroxy- $\beta$ -trifluoromethyl ketones, a standard protocol described by Crossland and Servis was employed to generate the corresponding enone: to a 0.2 M solution of starting material in dichloromethane was added a 50 mol % excess of triethylamine at 0 to  $-10^\circ\text{C}$ , followed by a 10 % excess of methanesulfonyl chloride over a period of 5-10 min.<sup>145</sup> Stirring for 1 hour at room temperature followed by work-up afforded enone **30** (Scheme 4.12).



**Scheme 4.12: Preparation of the  $\beta$ -trifluoromethyl enone**

By extending this methodology, a 4-MeO-substituted aryl ketone (enone **31**) was prepared, which would be useful for understanding the effect a substituent on the phenyl group of the ketone imparts on both the rate of the reaction and the enantioselectivity (Scheme 4.13).

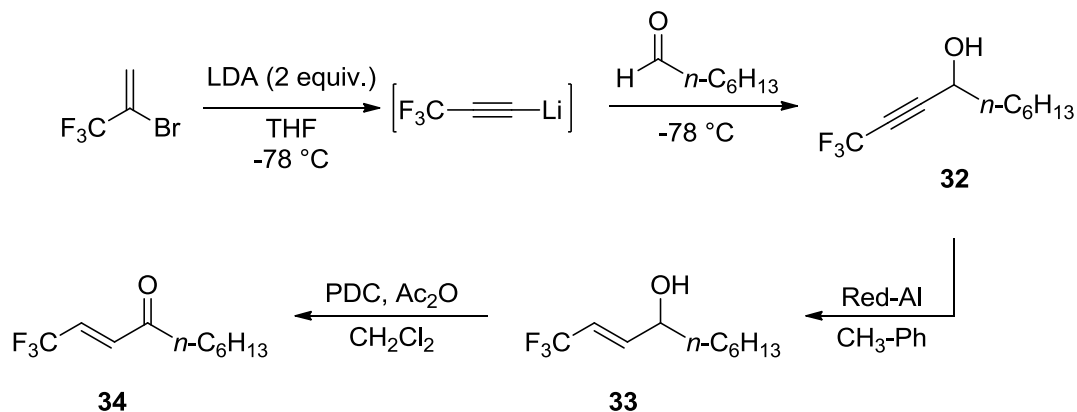


**Scheme 4.13: Preparation of enone 31**

However, the procedure developed by Funabiki and Matsui which employed the enamine or imine addition to trifluoroacetaldehyde ethyl hemiacetal was only useful for preparing  $\beta$ -trifluoromethyl enones derived from aryl ketones. We also wished to prepare  $\beta$ -trifluoromethyl ketones where the ketone substituent was a methyl group. Studying the additions of these various  $\beta$ -trifluoromethyl ketones would be vital to understanding what effect the substituent on the ketone has on both the rate of reaction and the enantioselectivity.

In 2004, Yamazaki and co-workers published a paper which included the synthesis of (*E*)-1,1,1-trifluorodec-2-en-4-one, a  $\beta$ -trifluoromethyl ketone derived from heptanal.<sup>146</sup> The synthesis began with mixing 2-bromo-3,3,3-trifluoro-1-propene with 2 equivalents of LDA (lithium diisopropylamide) to generate the corresponding lithium (trifluoromethyl)acetylide which was trapped with heptanal to furnish the respective alkynol.<sup>146</sup> Reduction of the alkynol with Red-Al

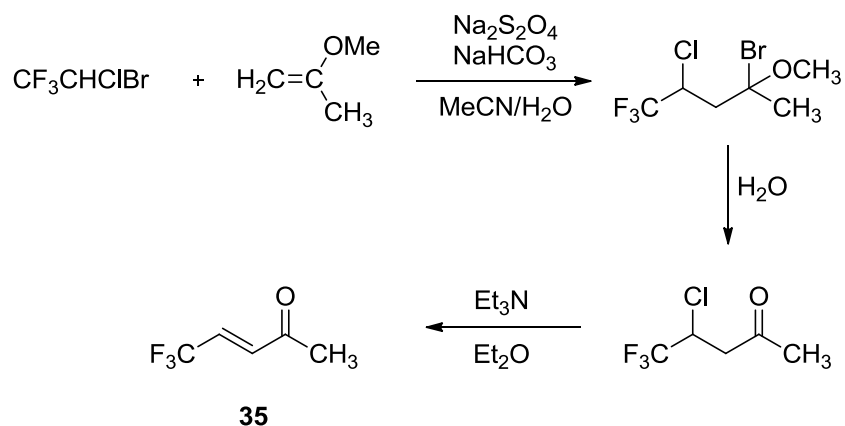
in toluene, followed by oxidation of the alcohol to the ketone furnished the  $\beta$ -trifluoromethyl ketone **32** (Scheme 4.14).<sup>146</sup>



**Scheme 4.14: Preparation of a  $\beta$ -trifluoromethyl ketone derived from heptanal**

Our initial efforts towards preparing enone **34** were unsuccessful. We were able to successfully prepare the alkynol **32**, but the subsequent reduction with Red-Al furnished what appeared to be the fully reduced analogue of **33** in the crude  $^1\text{H}$  NMR. We changed the aldehyde from heptanal to acetaldehyde, but were still unsuccessful in preparing the analogous enone.

An alternative procedure published by Dmowski and co-workers highlighted an efficient preparation of 5,5,5-trifluoro-3-penten-2-one via the sodium dithionite initiated addition of 1-bromo-1-chloro-2,2,2-trifluoroethane to 2-methoxypropene (Scheme 4.15).<sup>147</sup>

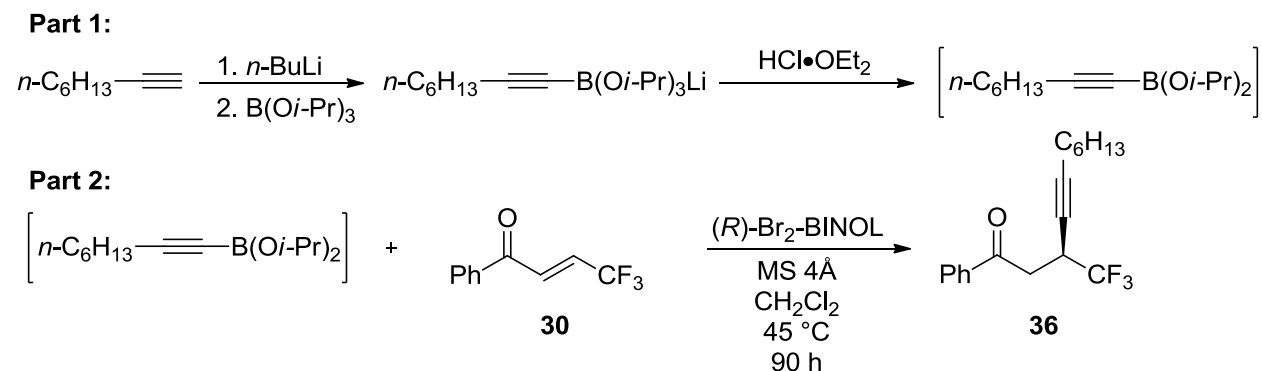


**Scheme 4.15: Preparation of aliphatic-based  $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated ketones**

The procedure was easy to follow and cleanly furnished enone **35** after distillation. With the three different enones **30**, **31** and **35** in hand, we began examining the reactivity of these substrates in the binaphthol-catalyzed conjugate additions.

### 4.3 Asymmetric Conjugate Alkynylation of $\beta$ -CF<sub>3</sub> Enones

Our efforts began by preparing the alkynylboronate nucleophile according to the one-pot method described by Wu and Chong.<sup>37</sup> To this alkynylboronate was added the enone **30**, molecular sieves, catalyst (*R*)-Br<sub>2</sub>-BINOL (0.2 mol %) and CH<sub>2</sub>Cl<sub>2</sub> (6 mL) (Scheme 4.16).



**Scheme 4.16: Asymmetric conjugate alkynylation of enone 30**

After stirring for 90 hours, an aliquot was taken from the reaction mixture and analyzed by  $^1\text{H}$  NMR. The crude  $^1\text{H}$  NMR indicated that the alkynylboronate had successfully added to the enone, generating adduct **36** with no visible trace of starting material **30** remaining.

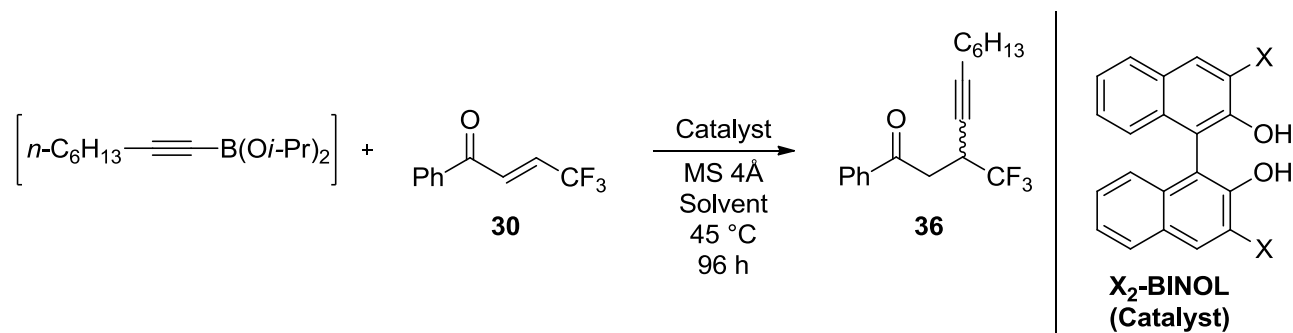
Encouraged by this initial result, we next wanted to examine to what extent changing the 3,3'-substituents on the binaphthol catalyst would have on the rate of reaction. We therefore examined (*R*)-Ph<sub>2</sub>-BINOL, (*S*)-CF<sub>3</sub>-BINOL and (*S*)-I<sub>2</sub>-BINOL as these catalysts were readily available, having previously been prepared. To our dismay, these reactions that employed alternative catalysts to (*R*)-Br<sub>2</sub>-BINOL were quite sluggish, with little adduct formed after refluxing for 4 days (Table 4.1, entries 2, 3, 4). Surprisingly, the (*R*)-Ph<sub>2</sub>-BINOL afforded a higher conversion rate of enone **30** to adduct **36**, as we had previously hypothesized that increasing the electron-withdrawing effect of the 3,3'-substituent would increase the rate of the reaction (Table 4.1, entries 2 and 3). Similarly, when (*S*)-I<sub>2</sub>-BINOL was employed with an increased solvent volume of 4 mL, the reaction rate was greater compared to when (*S*)-CF<sub>3</sub>-BINOL was employed, but no greater than when (*R*)-Ph<sub>2</sub>-BINOL was used (Table 4.1, entry 4).

A change to the racemic catalyst ( $\pm$ )-I<sub>2</sub>-BINOL accompanied with a decrease in the volume from 4 mL to 3 mL appeared to increase the rate of the reaction, with an observed ratio of 1:1.9 for enone **30** to adduct **36** in the crude  $^1\text{H}$  NMR after refluxing for 72 hours (Table 4.1, entry 5). It was hypothesized that this increase in reaction rate was a direct consequence of the increase in molarity of the reaction mixture.

After re-examination of the initial result, it was believed that the high conversion of enone **30** to adduct **36** was a result of an increase in the reaction molarity as it proceeded over a 4 day period. The alkynylboronate was prepared in a 25 mL round bottom flask, and to this was added the

enone and catalyst and 6 mL of solvent. The flask was fitted with a reflux condenser, and the septum at the top was sealed with a layer of parafilm. When the reaction was quenched after the 4 day period, a very minute amount of CH<sub>2</sub>Cl<sub>2</sub> remained in the flask. If the solvent had evaporated over the four day period as the reaction proceeded, the resulting increase in molarity would favour an increase in the rate of the reaction, thus explaining the high rate of conversion observed. Subsequent reactions employed a Schlenk tube (Table 4.1, entries 2, 3, 4, 5) to ensure no solvent escaped, and suffered from diminished reactivity compared to the initial result.

**Table 4.1: Summary of initial conjugate alkynylation screen**



Entry	Catalyst	Solvent	Molarity of Enone (mol/L)	% Conversion to <b>36</b>
1	( <i>R</i> )-Br <sub>2</sub> -BINOL	CH <sub>2</sub> Cl <sub>2</sub>	0.075	100
2	( <i>R</i> )-Ph <sub>2</sub> -BINOL	CH <sub>2</sub> Cl <sub>2</sub>	0.10	25
3	( <i>S</i> )-CF <sub>3</sub> -BINOL	CH <sub>2</sub> Cl <sub>2</sub>	0.10	45
4	( <i>S</i> )-I <sub>2</sub> -BINOL	CH <sub>2</sub> Cl <sub>2</sub>	0.075	34
5 <sup>a</sup>	(±)-I <sub>2</sub> -BINOL	CH <sub>2</sub> Cl <sub>2</sub>	0.10	34
6 <sup>b</sup>	( <i>S</i> )-I <sub>2</sub> -BINOL	CH <sub>3</sub> Ph	0.12	40
7 <sup>b</sup>	( <i>S</i> )-I <sub>2</sub> -BINOL	CF <sub>3</sub> Ph	0.15	100
8 <sup>a, b</sup>	( <i>S</i> )-I <sub>2</sub> -BINOL	B(OMe) <sub>3</sub>	0.10	8

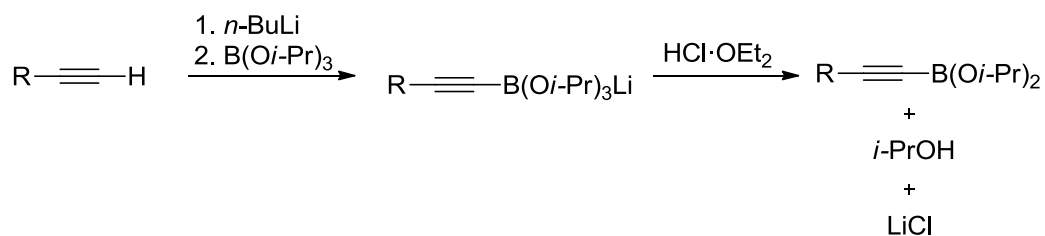
<sup>a</sup> Reaction checked after 72 hours. <sup>b</sup> Reaction temperature of 70 °C



After no significant change was observed by varying the 3,3'-substituents on the binaphthol or the molarity of the reaction, the next approach was to screen different solvents. Toluene was chosen as the first solvent to be screened, with a reaction temperature of 70 °C (Table 4.1, entry 6) and a solvent volume of 2.5 mL. After 3 days, a ratio of 1.5:1 of adduct **36** to enone **30** was observed in the crude <sup>1</sup>H NMR.  $\alpha, \alpha, \alpha$ -Trifluorotoluene was subsequently examined due to its similarity to dichloromethane due to a comparable dielectric constant, but higher boiling point allowing for more flexibility in reaction temperature. The reaction with 2 mL of trifluorotoluene and a temperature of 70 °C was complete after 4 days, with no visible trace of enone **30** in the crude <sup>1</sup>H NMR (Table 4.1, entry 7). This result was very encouraging as we had observed identical reactivity to the initial result (Table 4.1, entry 1) while maintaining the molarity of the reaction. Lastly, we screened trimethyl borate, as it is known to be a non-coordinating polar-aprotic solvent, which should help to stabilize the developing charges in the transition state, thus lowering the energy of the transition state and facilitating the conjugate addition. When 3 mL of trimethyl borate was employed with a temperature of 70 °C, an 11:1 ratio of enone **30** to adduct **36** was observed in the <sup>1</sup>H NMR after 3 days (Table 4.1, entry 8).

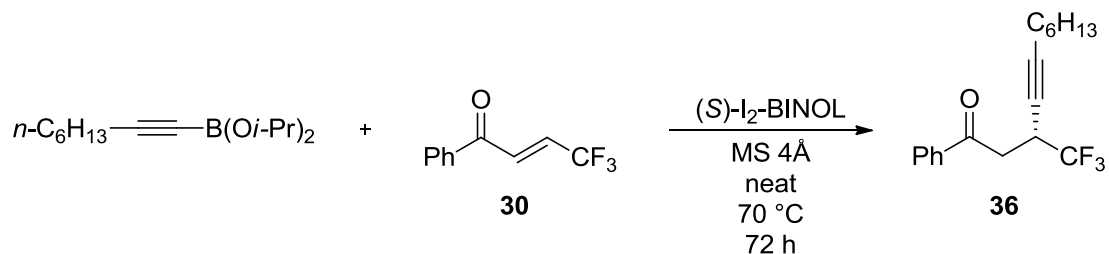
In an effort to further increase the reactivity, we decided to try running the reactions in the absence of solvent, solvating the enone, catalyst and molecular sieves in an excess of boronate. Prior to this, the solvent was required for transferring the solidified alkynylboronate-LiCl mixture to the Schlenk tube in which the reaction was run.

The alkynylboronates were no longer prepared via the one-pot procedure as previously described; instead, a procedure described by Brown and co-workers was used where the LiCl is removed by filtration, and the alkynylboronate is stored over molecular sieves (Scheme 4.17).<sup>148</sup>



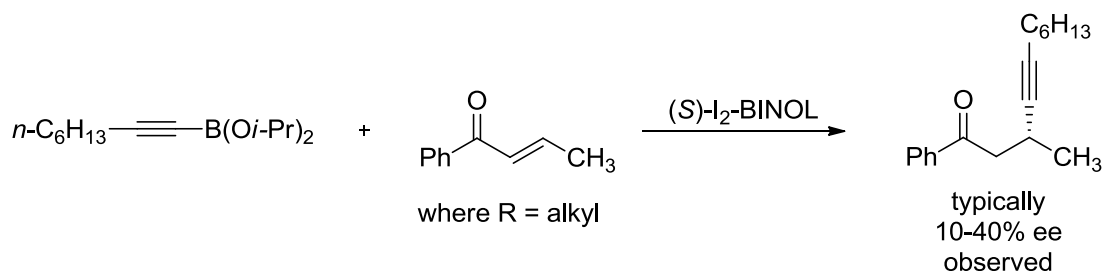
**Scheme 4.17: Preparation of lithium triisopropoxyalkynylboronates**

The initial temperature used in these new conditions was 70 °C, as this temperature was found to be the most effective for the conjugate alkynylation with trifluorotoluene (Table 4.1, entry 7). The initial reaction employing this new procedure was set up in a Schlenk tube and left to stir at 70 °C for 3 days (Scheme 4.18)



**Scheme 4.18: Asymmetric conjugate alkynylation of CF<sub>3</sub> enone 30 in the absence of solvent**

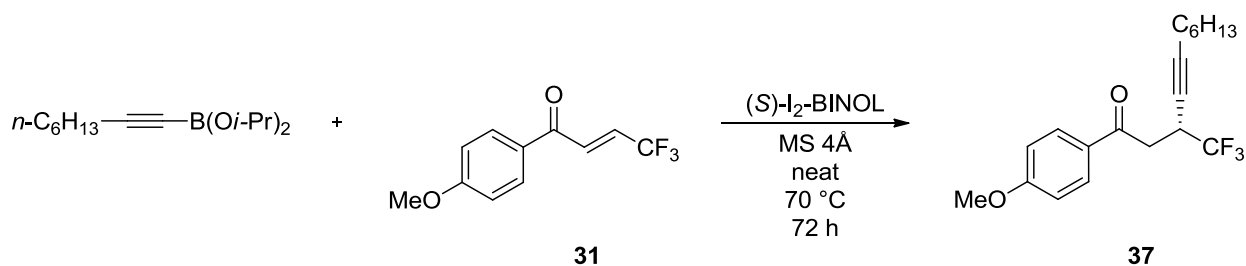
This refined method furnished the addition product **36** in 93% yield after a period of 3 days. Analysis by chiral HPLC indicated that the enantiomeric ratio of the reaction was 69:31. The enantioselectivity of this reaction is quite similar to what was observed in the conjugate alkynylation of β-alkyl enones reported by Wu and Chong (Scheme 4.19).



**Scheme 4.19: Comparing the alkynylation of enone **30** with  $\beta$ -alkyl substituted enones**

The conjugate alkynylation gives good selectivities for substrates bearing an aryl group in the  $\beta$ -position. For example, when the  $\beta$ -substituent was a phenyl or naphthyl group, the observed enantioselectivities were 86% and 96%, respectively. From this, we can conclude that the  $\text{CF}_3$  group in the  $\beta$ -position behaves much like an alkyl group. It is hypothesized that the large difference in stereoselectivity is due to the presence of an extended pi system in the case of the  $\beta$ -aryl substituents, which works to increase the selectivity in a manner which is not currently understood.

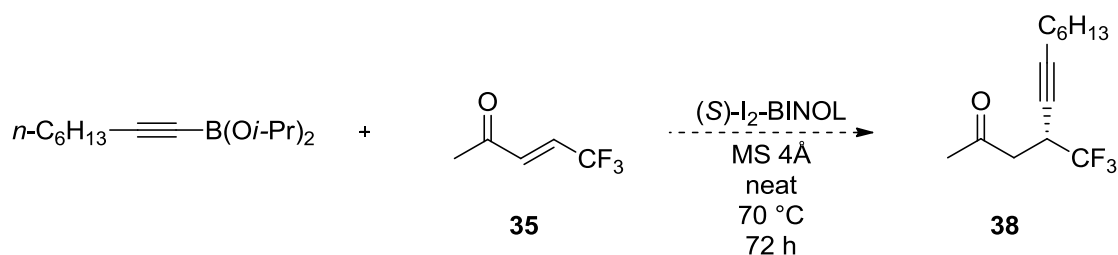
We next screened enone **31** in the asymmetric conjugate addition to examine what effect an electron-donating group in the *para*-position of the aryl group of the ketone has on the reactivity and enantioselectivity (Scheme 4.20).



**Scheme 4.20: Conjugate alkynylation of enone **31****

The addition product was isolated in 84% yield, and analysis by chiral HPLC indicated that the enantiomeric ratio of the reaction was 60:40, which was significantly lower than the enantioselectivity observed in the conjugate alkynylation of enone **30**. As it is not well understood whether or not this result is an outlier, the reaction will be repeated.

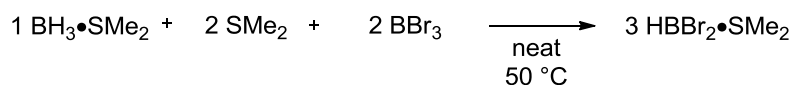
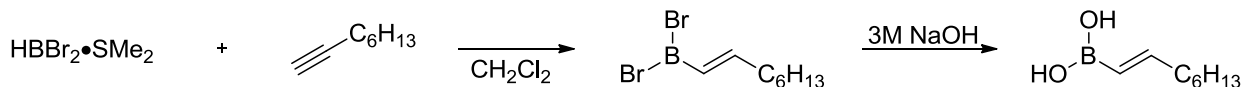
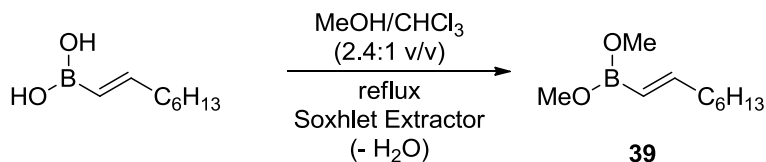
Moving forward, enone **35** will be examined in the asymmetric conjugate alkynylation to understand to what extent an alkyl-substituent on the ketone of the enone has on the enantioselectivity, and to compare this result with the selectivities observed with enones **30** and **31** (Scheme 4.21).



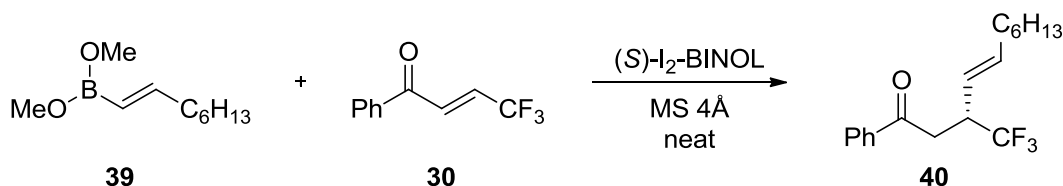
**Scheme 4.21: Next substrate to be examined in the asymmetric conjugate alkynylation**

#### 4.4 Asymmetric Conjugate Alkenylation of $\beta\text{-CF}_3$ Enones

Excited from the success of the alkynylation chemistry, we turned our attention to developing the asymmetric conjugate alkenylation chemistry which had been previously developed in our laboratory for  $\beta$ -aryl and alkyl ketones. The preparation of the alkenylboronate was straightforward, as it was previously outlined in a report by Batey and co-workers.<sup>149</sup> The alkenylboronate we chose for the initial screen was derived from 1-octyne, and its preparation is outlined below (Scheme 4.22).

**Part 1:****Part 2:****Part 3:****Scheme 4.22: Preparation of the alkenylboronate**

The initial screen employed the conditions previously developed in our group by Wu and Chong, with the only modification that the reactions were run neat, in the absence of solvent.<sup>41</sup> The substrate first chosen for the screen was enone **30** (Scheme 4.23).

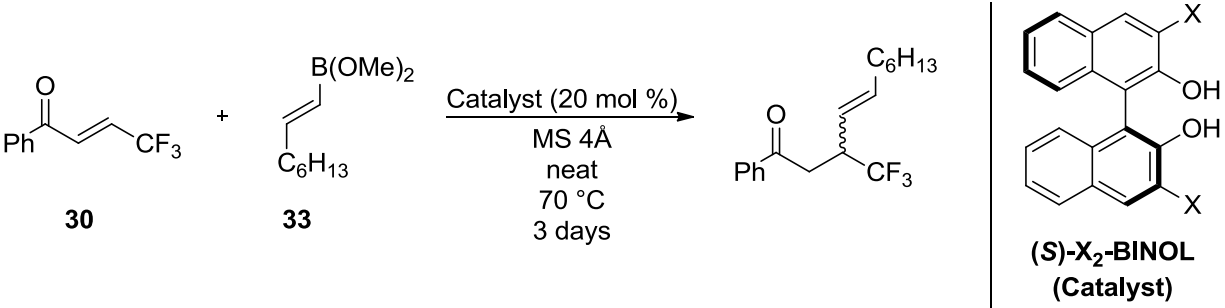
**Scheme 4.23: Conjugate alkenylboration of enone 30**

The reaction progress was monitored by taking aliquots of the reaction mixture and analyzing them by <sup>1</sup>H NMR. The initial temperature chosen to run the reaction at was 50 °C. After 24 hours, analysis by <sup>1</sup>H NMR revealed the reaction had barely progressed, with a vast majority of the reaction mixture consisting of enone **30**. To drive the reaction forward, the temperature was raised from 50 °C to 70 °C. Subsequent analysis of the reaction mixture at 48 hours indicated a ratio of 1.4:1 of adduct **40** to enone **30**. Although the conversion had been less than ideal, the

adduct was isolated and subjected to chiral HPLC analysis, which indicated an enantiomeric ratio of 96:4 for the reaction.

To examine the effect of the catalyst on the enantioselectivity, we screened various 3,3'-disubstituted binaphthol ligands (Table 4.2). The results of this catalyst screen would indicate the optimal catalyst for use in subsequent additions with different  $\beta$ -trifluoromethyl ketones. It was anticipated that the 3,3'-I<sub>2</sub>-BINOL would be the optimal catalyst, as it had previously been demonstrated by our lab to be the optimal catalyst in the binaphthol-catalyzed conjugate alkenylation and alkynylation.

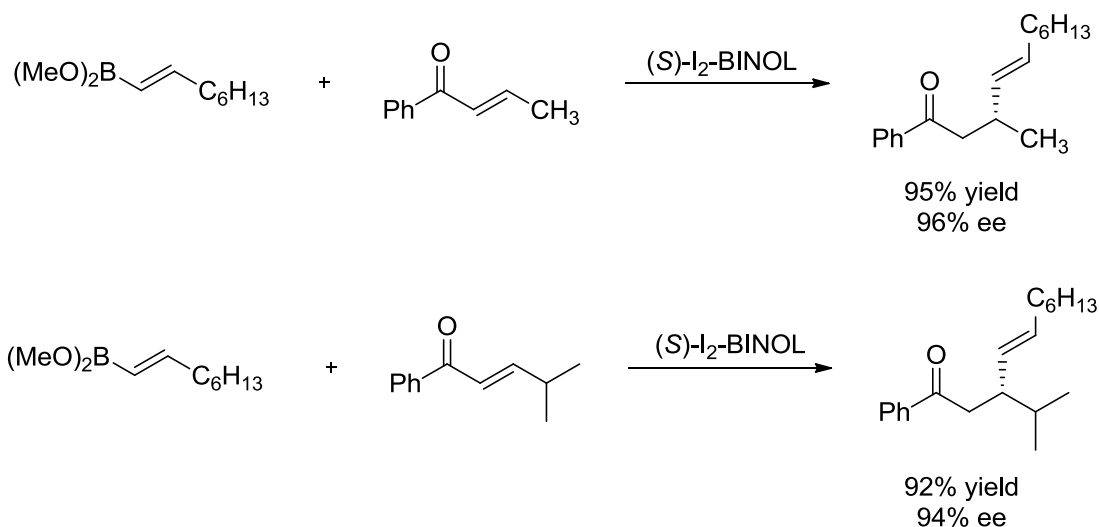
**Table 4.2: Catalyst screen in the asymmetric conjugate alkenylation to enone 30**

			
Entry	X (Ligand)	Yield (%) <sup>a</sup>	er <sup>b</sup>
1	I	86	96:4
2	Cl	96	91:9
3 <sup>c</sup>	Br	97	94:6
4	CF <sub>3</sub>	98	95:5
5 <sup>c</sup>	Ph	60	85:15

<sup>a</sup> Isolated yields after chromatography. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> (R)-X<sub>2</sub>-BINOL used.

The results of the catalyst screen confirmed our hypothesis that (*S*)-I<sub>2</sub>-BINOL would deliver the highest enantiomeric ratio. It was also apparent that both the steric and electronic character of the 3,3'-substituent affected both the rate of the reaction and the enantioselectivity. The halogen-substituted binaphthols all gave comparable yields, with a slight variation in the enantioselectivity. (*S*)-CF<sub>3</sub>-BINOL furnished the addition product in excellent yield and a good enantioselectivity due to the electron-withdrawing nature and steric bulk of the CF<sub>3</sub> substituent. On the other hand, the reaction with (*S*)-Ph<sub>2</sub>-BINOL suffered from a low chemical yield, presumed to be caused by the absence of any electron-withdrawing ability of the phenyl-substituent. Additionally, the observed enantioselectivity was the lowest of all the ligands screened. We hypothesized that the phenyl-substituent was too large, and imparted a steric repulsion in both diastereomeric transition states to some extent, decreasing the energy difference between the two transition states, lowering the enantioselectivity. (*S*)-I<sub>2</sub>-BINOL was rationalized to have the best compromise between size and electronic nature among all catalysts screened. As a result of the high enantiomeric ratio observed, it was used as the catalyst for subsequent investigations.

Comparing the result obtained with the (*S*)-I<sub>2</sub>-BINOL catalyst (Table 4.2, entry 1) with those obtained in the previously reported conjugate alkenylation of the β-CH<sub>3</sub> and β-*i*-Pr enones by Wu and Chong, the observed enantioselectivity with enone **30** is quite comparable to that observed with the β-CH<sub>3</sub> and β-*i*-Pr enones enones, indicating that the β-CF<sub>3</sub> enone **30** behaves much like an alkyl group (Scheme 4.24).

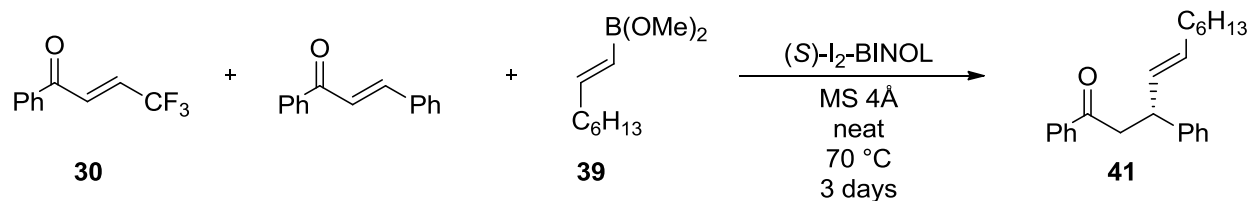


**Scheme 4.24: Comparing the conjugate alkenylation of enone **30** to similar enones**

Additionally, the enantioselectivity observed for the alkenylation of enone **30** is much different than what was observed in the conjugate alkynylation of enone **30**. This can be attributed to a difference in the nucleophile: the alkynylboronate is linear and geometrically similar to an arrow. Conversely, the alkenylboronate is geometrically larger; the (*E*)-geometry of the nucleophile confers a significant steric interaction in the transition state, leading to a higher difference in energy between the two diastereomeric transition states, which in turn increases the enantioselectivity.

We wanted to quantitate the difference in reactivity between (*E*)-chalcone and enone **30** to understand the difference in reactivity between different  $\beta$ -substituted ketones. A competition experiment was set up by mixing equimolar amounts of enone **30**, chalcone and the C<sub>8</sub>-alkenylboronate **33** (Scheme 4.25).

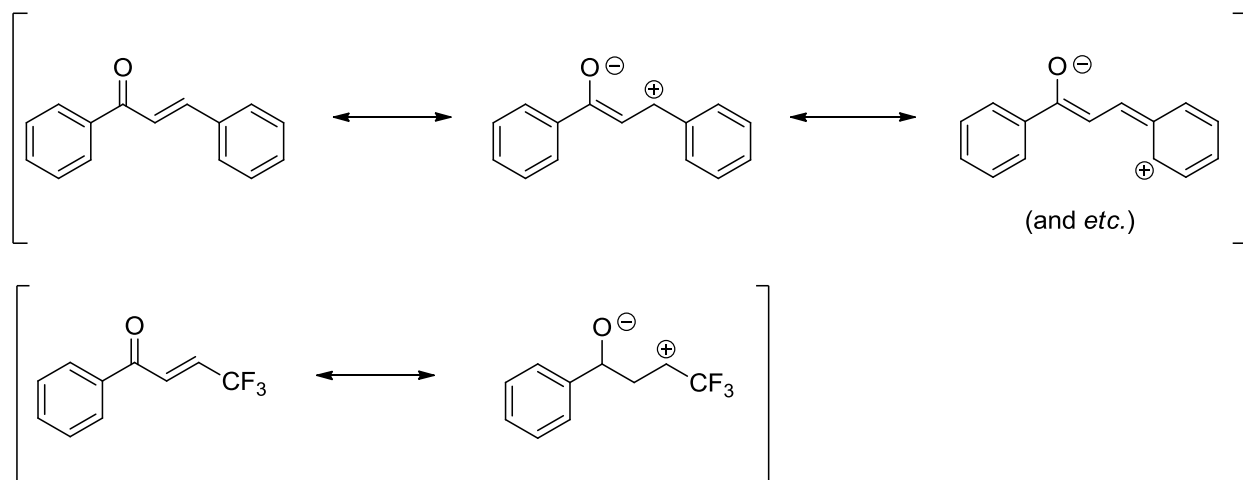




**Scheme 4.25: Competition experiment between  $\text{CF}_3$  enone **30** and chalcone**

The reaction was left to stir for 3 days, and then quenched by addition of MeOH. Standard work-up procedure and analysis of the crude  $^1\text{H}$  NMR revealed the exclusive formation of adduct **41**. If one assumes the limit of detection of  $^1\text{H}$  NMR with a 300 MHz instrument is 1%, we can deduce that the exclusive observation of adduct **41** with no visible trace of the other addition product would represent the rate of reaction of chalcone is at least 100 times faster than that of  $\beta$ -trifluoromethyl enone **30**.

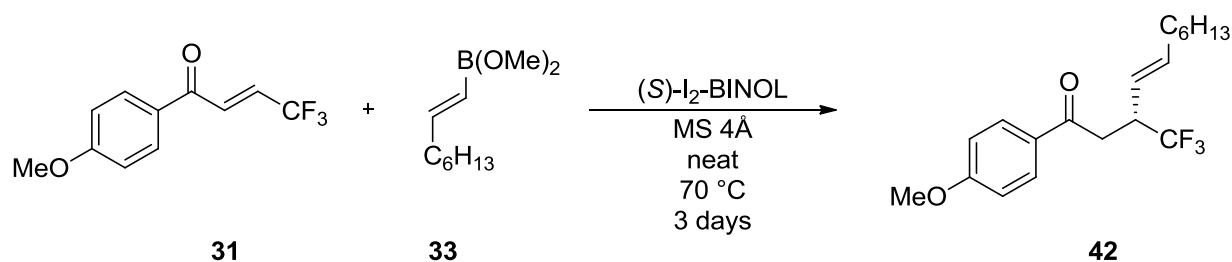
Previous studies of the alkynylboration by Wu and Chong revealed that the overall reaction rate is dependent on the  $\beta$ -substituent of the enone.<sup>37</sup> By examining the resonance structures of the enone, it can be understood why the reaction with chalcone is much faster than that with  $\beta$ -trifluoromethyl enone **30**: the positive charge in one of the resonance structures of chalcone can be delocalized around the phenyl substituent, thus helping to stabilize the charge. However, in the  $\beta$ -trifluoromethyl enone **30**, that same positive charge is adjacent to an electron withdrawing group, which is a destabilizing effect (Figure 4.2).



**Scheme 4.26: Resonance structures of  $\beta$ -trifluoromethyl enone **30** and chalcone**

By applying this same logic to the transition state of the conjugate addition of chalcone, the developing charges in the activated complex of chalcone are stabilized by that phenyl substituent, which in turn lowers the energy of the transition state. With less of an energy barrier to overcome, the conjugate addition of chalcone has a faster rate of reaction than the conjugate addition with  $\beta$ -trifluoromethyl enone **30**.

To better understand the conjugate alkenylboration of  $\beta$ -CF<sub>3</sub> enones, we mixed enone **31** with alkenylboronate **36** in the presence of a catalytic amount of (*S*)-I<sub>2</sub>-BINOL. After a reaction time of 3 days, the addition product was isolated in 81% yield, with an enantiomeric ratio of 96:4 (Scheme 4.27).



**Scheme 4.27: Conjugate alkenylation of enone **31****

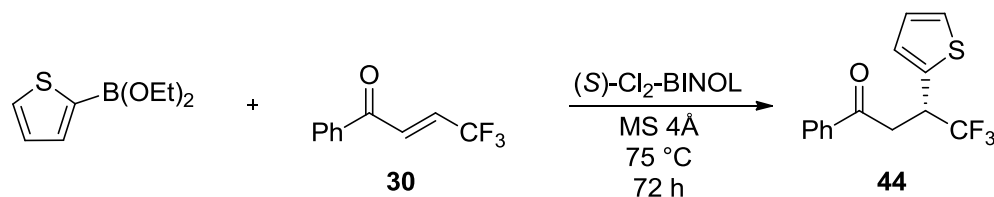
**43** + **33**  $\xrightarrow{(S)\text{-I}_2\text{-BINOL}}$  Product (86% yield, 98% ee)

The next steps in this study of the conjugate alkenylation chemistry will examine the conjugate alkenylation of enone **35**, comparing both the chemical yields and enantioselectivities with this substrate to that of enones **30** and **31**. Furthermore, the conjugate alkenylation using the 3,3'-Ph<sub>2</sub>-BINOL catalyst could be repeated to determine if the observed selectivity was accurate or just an anomaly of the reaction.

Diethyl thiophen-2-ylboronate and other heteroarylboronates have previously been shown to undergo asymmetric conjugate additions quite readily by Cheung and Chong.<sup>150</sup> Additionally, the reactions are run neat, using an excess of the diethyl thiophen-2-ylboronate as the solvent. This increase in the molality of the reaction mixture has previously been shown to increase the

rate of reaction in the binaphthol-catalyzed conjugate arylation chemistry developed by Turner and Chong.<sup>42</sup>

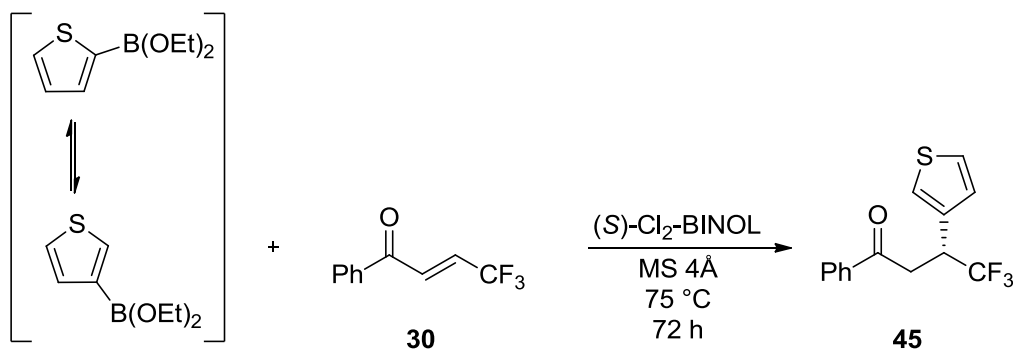
For our initial screen for the heteroarylation of enone **30**, the reaction was set-up identical to the procedure reported by Cheung and Chong (Scheme 4.29).<sup>150</sup>



**Scheme 4.29: Asymmetric conjugate addition of diethyl thiophen-2-ylboronate**

The crude  $^1\text{H}$  NMR of the reaction mixture after 36 hours at  $75\text{ }^\circ\text{C}$  showed an 8:1 ratio of starting material to addition product **44**. In an attempt to increase the reactivity, we set up the same reaction in both a  $100\text{ }^\circ\text{C}$  and  $120\text{ }^\circ\text{C}$  bath.

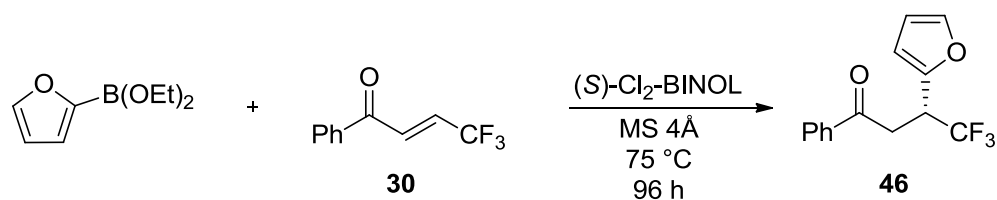
At  $100\text{ }^\circ\text{C}$ , the crude  $^1\text{H}$  NMR showed a 1:1 ratio of starting material to addition product **44** after 36 hours, indicating that the temperature increase had increased the reactivity. The reaction was quenched after 72 hours, and after standard work-up procedure, the product was isolated and characterized by  $^1\text{H}$  NMR. In the  $^1\text{H}$  NMR of the purified product, there were two identical multiplets at 4.6 and 4.4 ppm, with a ratio of 4:1 between them. These multiplets belong to the hydrogen that is on the  $\beta$ -carbon of the addition product. Re-evaluation of the  $^1\text{H}$  NMR of the  $75\text{ }^\circ\text{C}$  reaction also revealed the presence of the two multiplets. We hypothesized that the additional multiplet at 4.4 ppm belonged to an extra addition product, which could stem from an isomerization of the diethyl thiophen-2-ylboronate to diethyl thiophen-3-ylboronate (Scheme 4.30).



**Scheme 4.30: Hypothesized origin of the extra addition product**

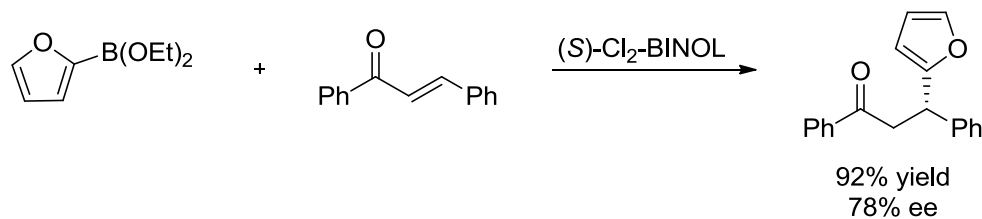
The crude  $^1\text{H}$  NMR of the reaction run at 120 °C indicating what we expected to be complete conversion of enone **30** to adduct **44** after a period of 84 hours. Although the rate of reaction had increased dramatically, the two multiplets stemming from what we believed to be two addition products were still present, in a ratio of 4.8:1 for the multiplets at 4.6 and 4.0 ppm respectively in the purified mixture. Unable to separate the two compounds by column chromatography or radial chromatography, we performed chiral HPLC analysis on the mixture and observed two sets of peaks in both the racemate and enantiopure product, with an enantiomeric excess of 22% for the reaction run with (*S*)-Cl<sub>2</sub>-BINOL.

Due to the difficulty in separating the mixture of addition products for the conjugate thiophenylation, we decided to turn to the diethyl furan-2-ylboronate which had also been shown to readily proceed in the binaphthol-catalyzed conjugate addition by Cheung and Chong (Scheme 4.31).<sup>150</sup>



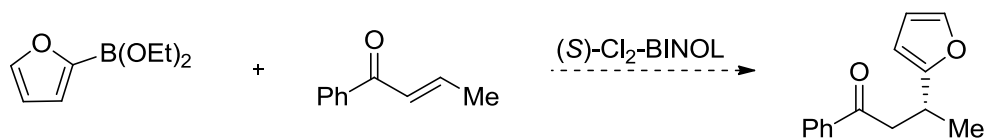
**Scheme 4.31: Addition of diethyl furan-2-ylboronates to  $\beta$ -CF<sub>3</sub> enones**

Based on our prior experience with the conjugate addition of diethyl thiophen-2-yl boronate which was incomplete after 72 hours, we decided to let the reaction with diethyl furan-2-yl boronate stir for an extra day. After 96 hours, the reaction was quenched and the addition product was isolated in 60% yield. Analysis by chiral HPLC chromatography indicated an enantiomeric ratio of 77:23. Comparing this result to the phenylboration reported by Cheung and Chong, the addition to the  $\beta$ -phenyl enone gave a higher yield and enantiomeric ratio (Scheme 4.32).



**Scheme 4.32: Comparison between the furanylation of different enones**

To better understand the enantioselectivity observed in the addition illustrated in Scheme 4.31, one should prepare the  $\beta$ -methyl substituted enone and examine what the observed enantioselectivity is in the addition of diethyl furan-2-yl boronate (Scheme 4.33).

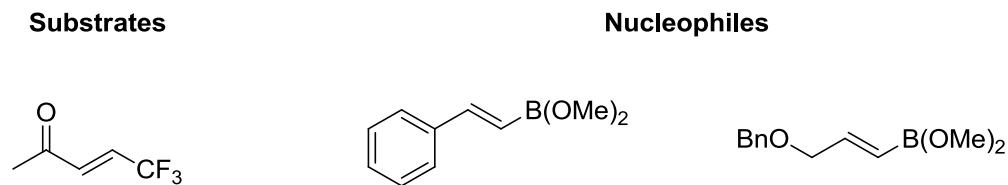


**Scheme 4.33: Future work in the conjugate addition of diethyl furan-2-yl boronate**

## 4.6 Summary and Future Work

In summary, we have accomplished the asymmetric conjugate addition of alkenyl-, alkynyl- and furan-2-ylboronates to β-trifluoromethyl α,β-unsaturated ketones. These efforts are the first methods for adding boronates to β-trifluoromethyl α,β-unsaturated ketones.

Future work will entail optimizing these reactions, increasing the scope of nucleophiles that can be added, and examining the effect different substrates have on the enantioselectivity for the conjugate alkenyl-, alkynyl-, and heteroarylations (Scheme 4.34).



**Scheme 4.34: Future studies in the conjugate additions to β-CF<sub>3</sub> enones**

Furthermore, the enantioselectivity of the furanylation of β-alkyl enones should be substantiated. Additionally, a deeper examination into the thiophenylation is necessary in an effort to minimize the formation of the side product arising from what appears to be the addition of the thiophen-3-ylboronate.

## 4.7 General Experimental

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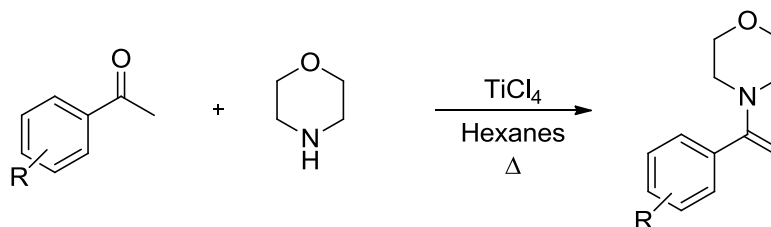
All reactions were performed using flame-dried glassware under an argon atmosphere. Solvents and solutions were transferred with syringes and cannulae using standard inert atmosphere techniques. Dichloromethane and hexanes were freshly distilled from calcium hydride. Molecular sieves (powder) were activated immediately prior to use. Chiral 3,3'-disubstituted binaphthols were synthesized using procedures from a previous report.<sup>38</sup> Alkenylboronates and arylboronates were all synthesized according to procedures from a previous report.<sup>41,42</sup> Alkynylboronates were prepared following a procedure developed by Brown.<sup>148</sup> Yields refer to chromatographically and spectroscopically pure materials unless otherwise stated. Reaction temperatures are reported as the temperature of the bath.

Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel 60 F<sub>254</sub> plates with visualization via short wave UV light or cerium ammonium molybdate staining. Flash chromatography was performed according to Still, and carried out using 40-63  $\mu$ m silica gel 60, eluting with solvents as indicated.<sup>151</sup> IR spectra were recorded as thin films between NaCl plates using dichloroethane (DCE) or chloroform (CHCl<sub>3</sub>) as the solvent for both liquids and solids. <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded in CDCl<sub>3</sub> at 300 MHz, 75 MHz, and 282 MHz respectively, and are referenced to CHCl<sub>3</sub> ( $\delta$  7.24), CDCl<sub>3</sub> ( $\delta$  77.0), or TFA ( $\delta$  -76.53), respectively. <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded with broad band proton decoupling. Multiplicities are reported as: ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, ap t = apparent triplet, m = multiplet, br = broad, td = triplet of doublets, quint d = quintet of doublets. Positive ion Electrospray (ESI) and Direct Analysis in Real Time (DART) experiments were performed with a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For



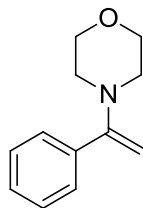
ESI, samples were infused at 5mL/min in 1:1 CH<sub>3</sub>OH/H<sub>2</sub>O+0.1% formic acid. For DART, samples were introduced in transmission mode employing metastable He at 150 °C for sample desorption/ionization. Optical rotations were recorded in cells with 10 cm path length on a Rudolph Autopol III digital polarimeter. Enantiomeric purities were determined by HPLC analysis (4.6 x 250 mm ChiralCel OD-H, hexane/*i*-PrOH, 254 nm detection).

**General Procedure for the Synthesis of Enamines:**<sup>144</sup>



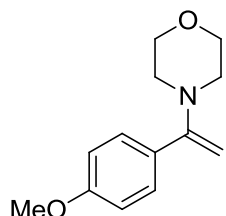
A 250 mL three-necked flask equipped with a dropping funnel, reflux condenser and nitrogen inlet was flame-dried and left to cool under argon. The flask was then charged with morpholine (4.6 eq., 0.23 mol, 20.1 mL) and 50 mL of hexanes. The reaction mixture was cooled to 0 °C with an ice-water bath. Titanium tetrachloride (0.7 eq., 0.035 mol, 3.9 mL) was dissolved in 20 mL of hexanes and added dropwise through the addition funnel. The funnel was rinsed with a further 10 mL of hexanes. After the addition was complete, the desired ketone (1 eq., 0.05 mol) was added in one portion. The bath was removed and the reaction was allowed to warm to room temperature, upon which the temperature was increased to reflux for 1 hour. After this time, the reaction was allowed to cool to room temperature and stirred overnight. The mixture was then filtered through a sintered glass funnel, and solvent removed by rotary evaporation under reduced pressure. The enamines were carried forward without purification.

#### 4-(1-phenylvinyl)morpholine



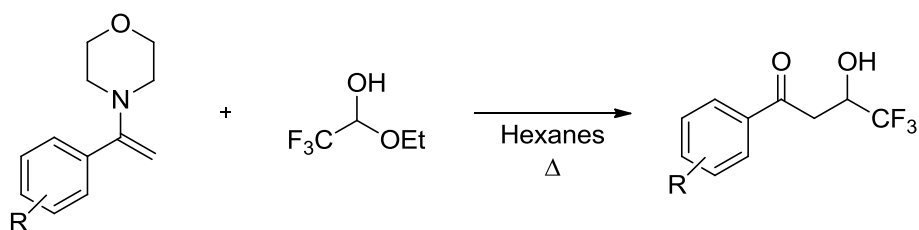
Prepared through condensation of morpholine with acetophenone (1 eq., 0.05 mol, 5.85 mL). The compound was in agreement with the reported spectral data.<sup>144</sup>

#### 4-(1-(4-methoxyphenyl)vinyl)morpholine



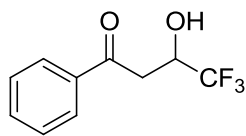
Prepared through condensation of morpholine with 4-methoxyacetophenone (1 eq., 0.05 mol, 7.5 g). The compound was in agreement with the reported spectral data.<sup>144</sup>

#### General Procedure for the Synthesis of $\beta$ -Hydroxy- $\beta$ -Trifluoromethyl Ketones:<sup>143</sup>



To a 250 mL flask containing a solution of the enamine (1 eq., 0.05 mol) in 100 mL of hexanes at room temperature was added trifluoroacetaldehyde ethyl hemiacetal (1 eq., 0.05 mol, 5.7 mL). The reaction mixture was warmed to reflux for 24 hours. The mixture was cooled to room temperature and 50 mL of 10% HCl was added and left to hydrolyze overnight. The mixture was transferred to a separatory funnel and extracted with diethyl ether (100 mL x 3), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary evaporation under reduced pressure. The crude material was carried forward without any purification.

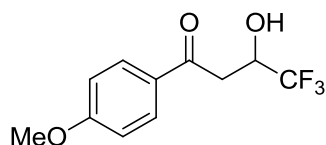
#### 4,4,4-trifluoro-3-hydroxy-1-phenylbutan-1-one



Spectral data for this compound were found to be in accordance with the previously reported spectra.<sup>143</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.97-7.99 (2H, m), 7.62-7.66 (1H, m), 7.49-7.53 (2H, m), 4.65-4.74 (1H, m), 3.47 (1H, d,  $J$  = 2.9 Hz), 3.39 (1H, dd,  $J$  = 17.9, 8.8 Hz), 3.33 (1H, dd,  $J$  = 17.9, 3.2 Hz).

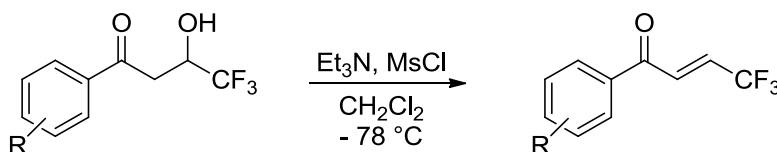
#### 4,4,4-trifluoro-3-hydroxy-1-(4-methoxyphenyl)butan-1-one



Spectral data for this compound were found to be in accordance with the previously reported spectra.<sup>143</sup>

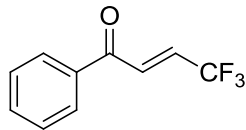
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.95 (2H, m), 6.97 (2H, m), 4.62-4.71 (1H, m), 3.90 (3H, s), 3.65 (1H, d,  $J$  = 4.4 Hz), 3.32 (1H, dd,  $J$  = 17.8, 8.0 Hz), 3.27 (1H, dd,  $J$  = 17.9, 4.2 Hz).

#### General Procedure for the Preparation of $\beta$ -Trifluoromethyl $\alpha,\beta$ -unsaturated Ketones:<sup>145</sup>



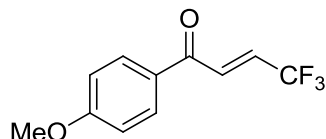
A 0.5 M solution of  $\beta$ -hydroxy- $\beta$ -trifluoromethyl ketone in methylene chloride and triethylamine (2 eq., 0.1 mol, 12 mL) was cooled to -78 °C in a dry ice/acetone bath. To this stirred solution was added methanesulfonyl chloride (2 eq., 0.1 mol, 6.8 mL) dropwise. After the addition, the bath was removed and the reaction was allowed to warm to room temperature and stirred overnight. The mixture was transferred to a separatory funnel and washed with water (100 mL) followed by 10% HCl (100 mL), saturated NaHCO<sub>3</sub> (100 mL) and finally brine (100 mL). The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary evaporation under reduced pressure. The enone was purified by chromatographic separation on silica gel eluting with a mixture of hexanes/ethyl acetate to furnish the addition product.

**(E)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (30)**



The compound was isolated after silica gel chromatography using 10:1 hexanes:EtOAc. Spectral data for this compound were found to be in accordance with the previously reported spectra.<sup>138</sup>

**(E)-4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-en-1-one (31)**

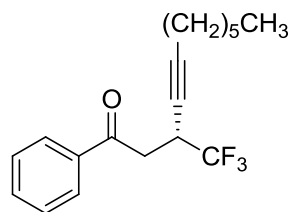


The compound was isolated after silica gel chromatography using 10:1 hexanes:EtOAc. Spectral data for this compound were found to be in accordance with the previously reported spectra.<sup>138</sup>

**General Procedure for the Conjugate Addition to  $\beta$ -CF<sub>3</sub>  $\alpha,\beta$ -unsaturated Ketones:**

To an oven-dried Schlenk tube was added 0.05 g of 4Å molecular sieves. The vessel was placed under vacuum and flame-dried for one minute to activate the sieves. The vessel was cooled under vacuum, during which the appropriate enone (0.3 mmol) and binaphthol (0.06 mmol) were weighed out. The vessel was placed under a positive pressure of argon, and the enone, binaphthol and a magnetic stirring bar were added. The vessel was evacuated and backfilled with argon for a total of three times. The appropriate boronate (4.5 mmol, 0.5 mL) was then added to the reaction mixture. The vessel was sealed and transferred to an oil bath pre-heated to 75 °C and left to stir until the reaction was complete. Afterwards, the vessel was removed from the bath, cooled to room temperature and methanol (0.5 mL) was added. The mixture was filtered through a 1 cm pad of Celite<sup>®</sup> which was rinsed with acetone, and concentrated by rotary evaporation. The crude material was then purified by flash chromatography on silica gel, eluting with a mixture of hexanes/ethyl acetate to furnish the addition product.

**(R)-1-phenyl-3-(trifluoromethyl)undec-4-yn-1-one (36)**

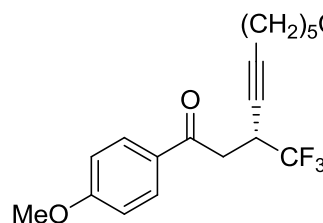


The compound was prepared in 93% yield as a yellow oil after silica gel chromatography using 30:1 hexanes:EtOAc.

$[\alpha]_D^{25} +6.5$  (69.3:30.7 er, c 2.0,  $\text{CHCl}_3$ ); **IR** (NaCl,  $(\text{CH}_2\text{Cl})_2$ ): 1694, 1449, 1429, 1285, 1233, 944, 882, 675  $\text{cm}^{-1}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (2H, d,  $J = 7.3$  Hz), 7.60 (1H, t,  $J = 7.3$  Hz), 7.48 (2H, t,  $J = 7.5$  Hz), 3.93 (1H, m), 3.46 (1H, dd,  $J = 17.1, 9.2$  Hz), 3.26 (1H, dd,  $J = 17.1, 3.9$  Hz), 2.10 (2H, dt,  $J = 6.8, 2.0$  Hz), 1.46-1.21 (8H, m), 0.84 (3H, t,  $J = 6.7$  Hz);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  194.9, 136.2, 133.7, 128.8, 128.2, 125.6 (q,  $^1J_{\text{C-F}} = 277.3$  Hz), 85.2, 72.6, 38.4, 33.2 (q,  $^2J_{\text{C-F}} = 31.3$  Hz), 31.2, 28.3, 22.5, 18.5, 13.9;  **$^{19}\text{F}$  NMR** (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -71.9; HRMS  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{21}\text{F}_3\text{O}$  ( $\text{M}^+$ ): 311.1617, found 311.1616.

The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 0.5 mL/min),  $t_R = 19.1$  min (*S*),  $t_R = 27.8$  min (*R*).

**(R)-1-(4-methoxyphenyl)-3-(trifluoromethyl)undec-4-yn-1-one (37)**

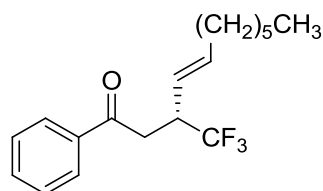


The compound was prepared in 84% yield as a yellow oil after silica gel chromatography using 30:1 hexanes:EtOAc.

$[\alpha]_D^{25} +13.7$  (60:40 er, c 1.66,  $\text{CHCl}_3$ ); **IR** (NaCl,  $(\text{CH}_2\text{Cl})_2$ ): 1683, 1449, 1430, 1285, 1233, 944, 881, 676  $\text{cm}^{-1}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (2H, d,  $J = 8.7$  Hz), 6.97 (2H, d,  $J = 8.7$  Hz), 3.95 (1H, m), 3.90 (3H, s), 3.42 (1H, dd,  $J = 17.0, 9.2$  Hz), 3.22 (1H, dd,  $J = 17.0, 3.8$  Hz), 2.13 (2H, t,  $J = 6.9$  Hz), 1.46-1.24 (8H, m), 0.86 (3H, t,  $J = 6.6$  Hz);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.3, 163.9, 130.5, 129.4, 125.6 (q,  $^1J_{\text{C-F}} = 277.4$  Hz), 113.9, 85.12, 72.8, 55.5, 38.0, 33.3 (q,  $^2J_{\text{C-F}} = 31.1$  Hz), 31.2, 28.3, 22.4, 18.5, 13.9;  **$^{19}\text{F}$  NMR** (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -71.9; HRMS  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{23}\text{F}_3\text{O}_2$  ( $\text{M}^+$ ): 341.1723, found 341.1722.

The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 0.5 mL/min),  $t_R = 44.9$  min (*S*),  $t_R = 50.0$  min (*R*).

**(R,E)-1-phenyl-3-(trifluoromethyl)undec-4-en-1-one (40)**



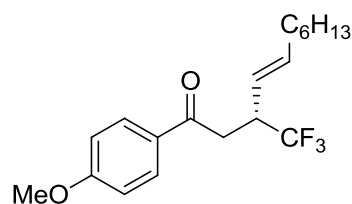
The compound was prepared in 86% yield as a pale yellow oil after silica gel chromatography using 30:1 hexanes:EtOAc.

$[\alpha]_D^{25} +12.5$  (96.5:3.5 er, c 1.06,  $\text{CHCl}_3$ ); **IR** (NaCl,  $\text{CHCl}_3$ ): 1694, 1598, 1450, 968, 753, 689  $\text{cm}^{-1}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.93 (2H, d,  $J = 7.5$  Hz), 7.57 (1H, t,  $J = 7.3$  Hz), 7.46 (2H, t,  $J = 7.5$  Hz), 5.72 (1H, dt,  $J = 15.3, 7.2$  Hz), 5.27 (1H, dd,  $J = 15.3, 8.4$  Hz), 3.61 (1H, app. sept.  $J = 7.7$  Hz), 3.22 (2H, d,  $J = 6.5$  Hz), 1.97 (2H, q,  $J = 6.8$  Hz), 1.24 (8H, m), 0.83 (3H, t,  $J = 6.5$  Hz);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.9, 138.2, 136.6, 133.5, 128.7, 128.1, 127.1 (q,  $^1J_{\text{C-F}} = 277.3$  Hz),

121.9, 42.5 ( $^2J_{\text{C-F}} = 27.2$  Hz), 37.2, 32.5, 31.6, 28.7, 28.6, 22.6, 14.0;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -71.5; HRMS  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{23}\text{F}_3\text{O}$  ( $\text{M}^+$ ): 313.1774, found 313.1773.

The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.9/0.1, flow rate = 0.5 mL/min),  $t_{\text{R}} = 36.7$  min (*S*),  $t_{\text{R}} = 40.5$  min (*R*).

**(*R,E*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)undec-4-en-1-one (42)**

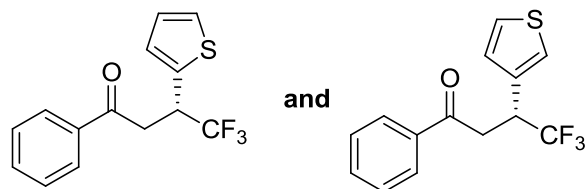


The compound was prepared in 81% yield as a yellow oil after silica gel chromatography using 30:1 hexanes:EtOAc.

$[\alpha]_{\text{D}}^{25} +49.6$  (95.7:4.3 er,  $c$  1.58,  $\text{CHCl}_3$ ); **IR** (NaCl,  $\text{CHCl}_3$ ): 1682, 1601, 1465, 907, 726, 672  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91 (2H, d,  $J = 8.6$  Hz), 6.93 (2H, d,  $J = 8.6$  Hz), 5.70 (1H, dt,  $J = 15.3$  Hz, 7.4 Hz), 5.26 (1H, dd,  $J = 15.3$  Hz, 8.6 Hz), 3.86 (1H, s), 3.58 (1H, m), 3.17 (2H, d,  $J = 7.3$  Hz), 1.96 (2H,  $J = 6.8$  Hz), 1.24 (8H, m), 0.82 (3H, t,  $J = 6.4$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  194.3, 163.8, 137.9, 130.4, 129.7, 127.1 (q,  $^1J_{\text{C-F}} = 277.3$  Hz), 122.1, 122.0, 113.8, 55.5, 42.6 (q,  $^2J_{\text{C-F}} = 27.1$  Hz), 36.8, 32.4, 31.6, 28.7, 28.6, 22.5, 14.0;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -71.5; HRMS  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{25}\text{F}_3\text{O}_2$  ( $\text{M}^+$ ): 343.1879, found 343.1880.

The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.7/0.3, flow rate = 0.25 mL/min),  $t_{\text{R}} = 72.0$  min (*R*),  $t_{\text{R}} = 79.3$  min (*S*).

**(*S*)-4,4,4-trifluoro-1-phenyl-3-(thiophen-2-yl)butan-1-one (44) and (*R*)-4,4,4-trifluoro-1-phenyl-3-(thiophen-3-yl)butan-1-one (45) mixture**

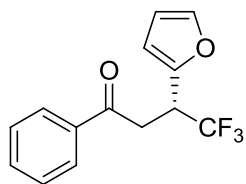


The mixture was obtained in 72% yield as a white solid after silica gel chromatography using 25:1 hexanes:EtOAc.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.92 (2H, d,  $J = 7.4$  Hz), 7.57 (1H, t,  $J = 7.3$  Hz), 7.45 (1H, t,  $J = 7.7$  Hz), 7.22 (1H, d,  $J = 5.3$  Hz), 7.08 (1H, d,  $J = 3.1$  Hz), 6.94 (1H, t,  $J = 4.2$  Hz), 4.58 (1H, quint. d,  $J = 3.8, 9.2, 9.1$  Hz), 4.40 (1H, quint. d,  $J = 4.6, 9.2, 9.2$  Hz), 3.67 (1H, dd,  $J = 17.7, 9.2$  Hz), 3.54 (1H, dd,  $J = 17.7, 3.9$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.0, 194.9, 142.7, 136.3, 136.2, 136.1, 133.7, 128.8, 128.1, 127.7, 126.9, 126.1 (q,  $^1J_{\text{C-F}} = 273.8$  Hz), 125.6, 124.2, 110.6, 109.4, 40.3 (q,  $^2J_{\text{C-F}} = 28.4$  Hz), 39.0 (q,  $^2J_{\text{C-F}} = 29.3$  Hz), 39.4, 35.9;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -70.4, -70.9.

The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.0 /1.0, flow rate = 0.5 mL/min), for **2-thienyl**  $t_{\text{R}} = 16.3$  min (*R*),  $t_{\text{R}} = 24.4$  min (*S*), for **3-thienyl**  $t_{\text{R}} = 17.7$  min (*R*),  $t_{\text{R}} = 22.9$  min (*S*).

**(R)-4,4,4-trifluoro-3-(furan-2-yl)-1-phenylbutan-1-one (46)**

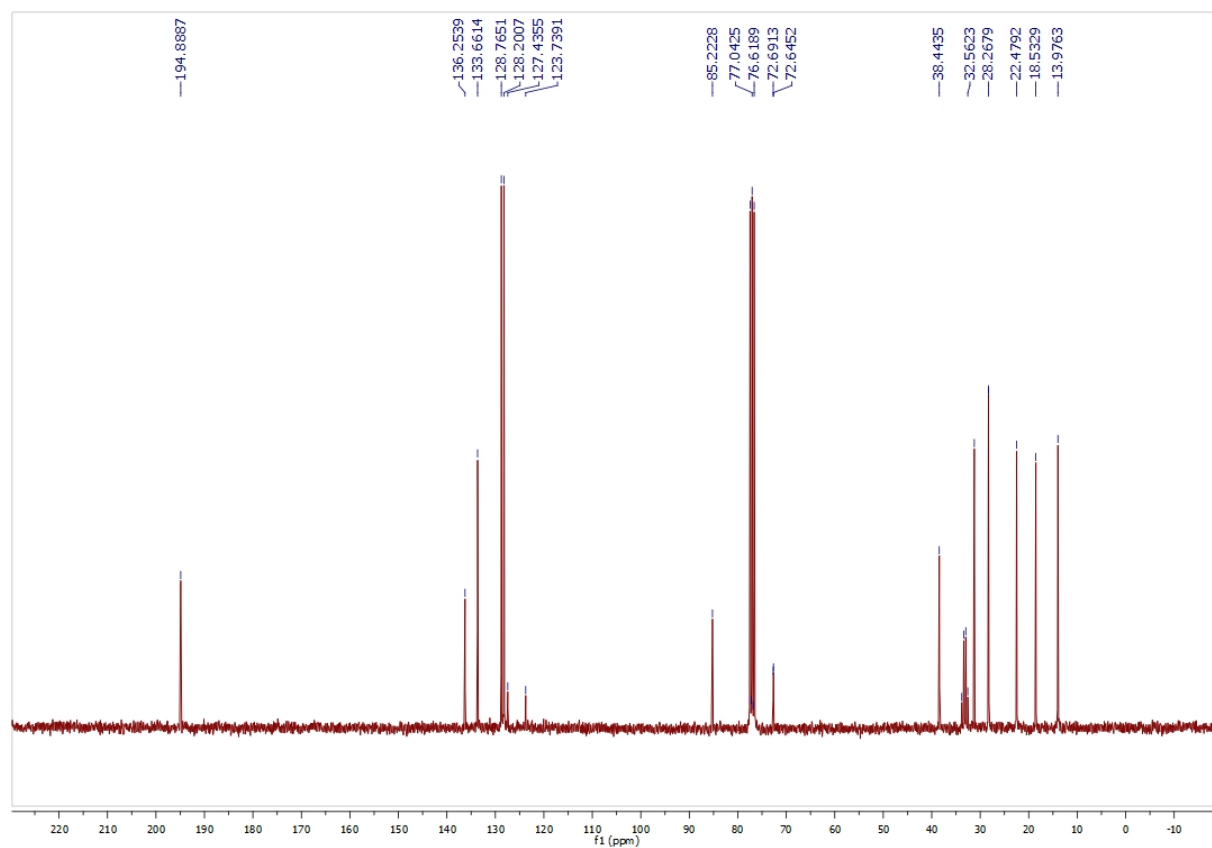
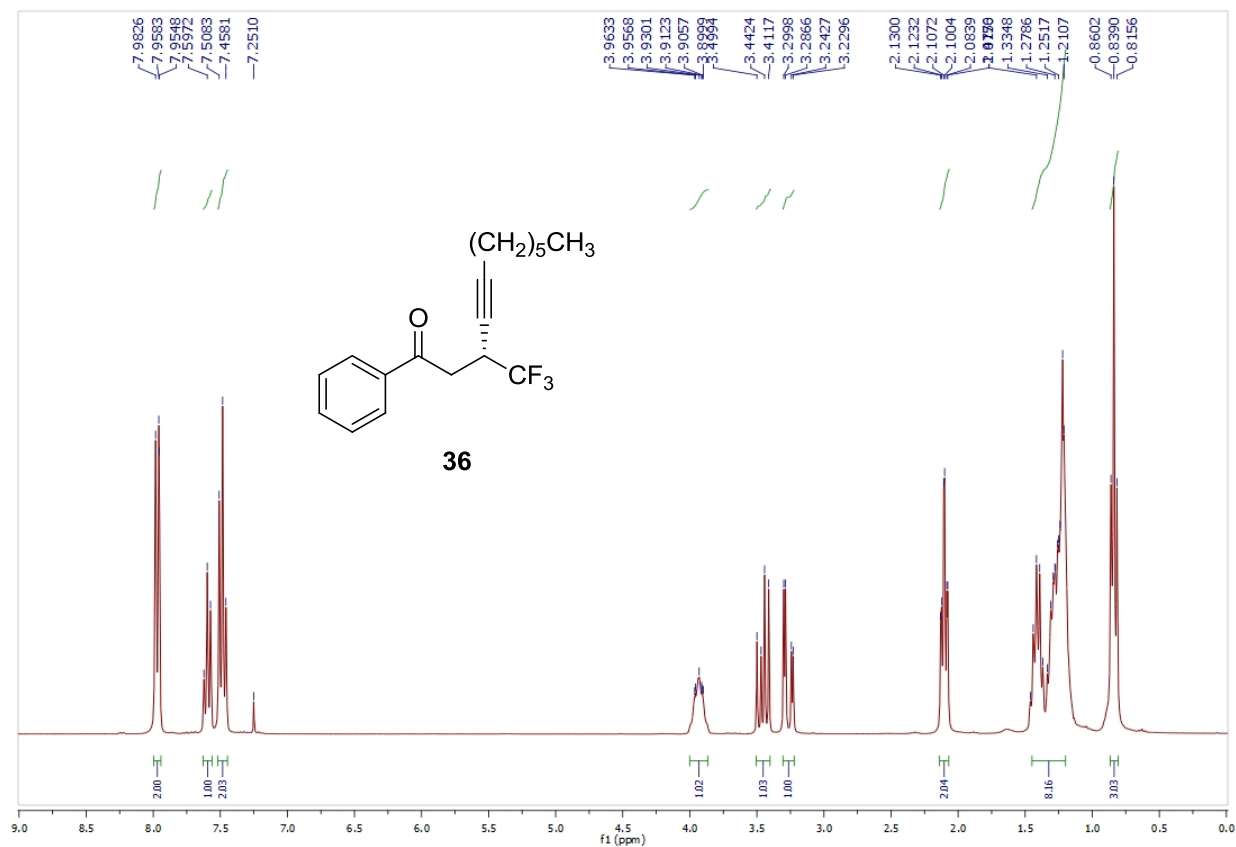


The mixture was obtained in 60% yield as a clear oil after silica gel chromatography using 25:1 hexanes:EtOAc.

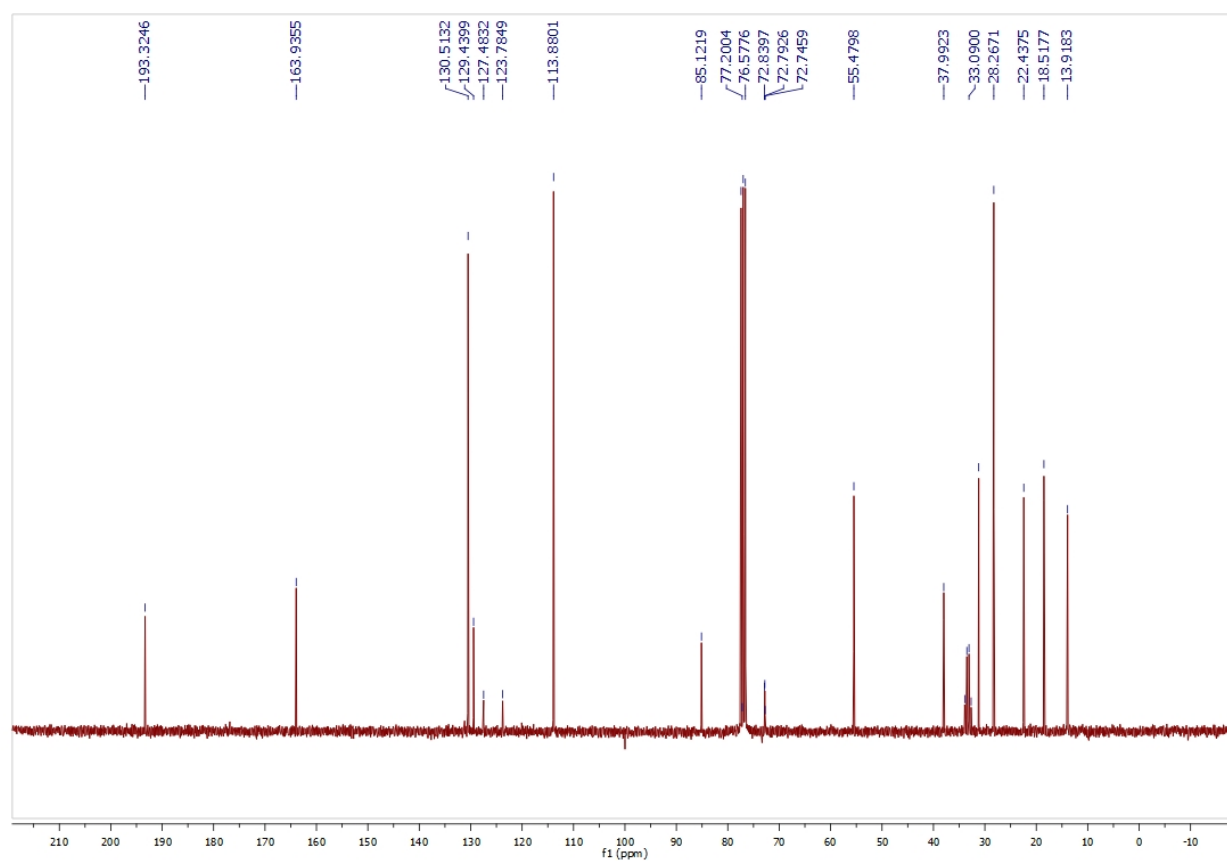
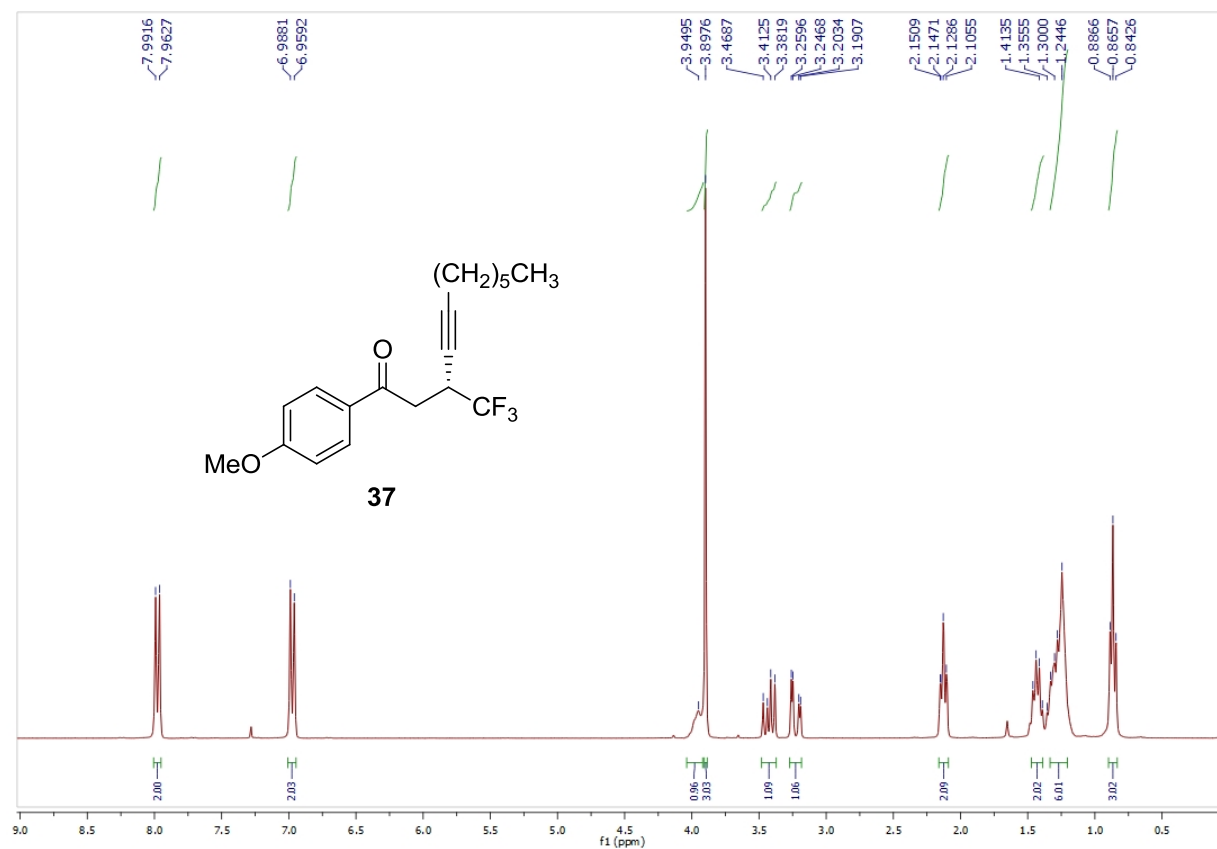
$[\alpha]_D^{25} +10.1$  (77.3:22.7  $\text{er}$ ,  $c$  0.9,  $\text{CHCl}_3$ ); **IR** ( $\text{NaCl}$ ,  $(\text{CH}_2\text{Cl})_2$ ): 1712, 1429, 1285, 1233, 944, 881, 711  $\text{cm}^{-1}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95 (2H, d,  $J = 7.7$  Hz), 7.58 (1H, t,  $J = 7.2$  Hz), 7.46 (2H, t,  $J = 7.4$  Hz), 7.34 (1H, s), 6.32 (2H, d,  $J = 2.9$  Hz), 4.41 (1H, m), 3.77 (1H, dd,  $J = 17.7, 9.5$  Hz), 3.45 (1H, dd,  $J = 17.7, 3.2$  Hz);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.0, 147.5, 142.7, 136.1, 133.7, 128.8, 128.1, 125.8 (q,  $^1J_{\text{C-F}} = 277.6$  Hz), 110.6, 109.4, 39.0 (q,  $^2J_{\text{C-F}} = 29.3$  Hz), 35.9;  **$^{19}\text{F}$  NMR** (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -70.5; HRMS  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{11}\text{F}_3\text{O}_2$  ( $\text{M}^+$ ): 269.0784, found 269.0785.

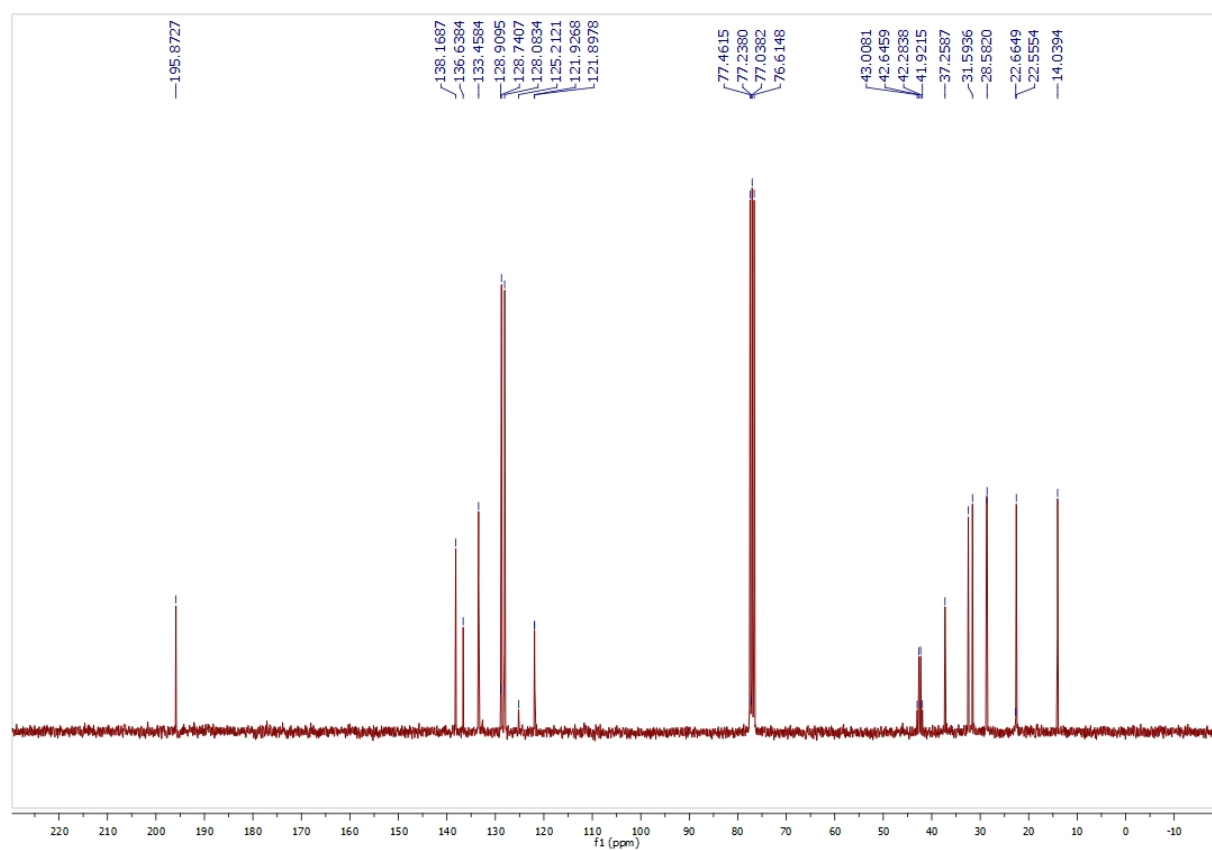
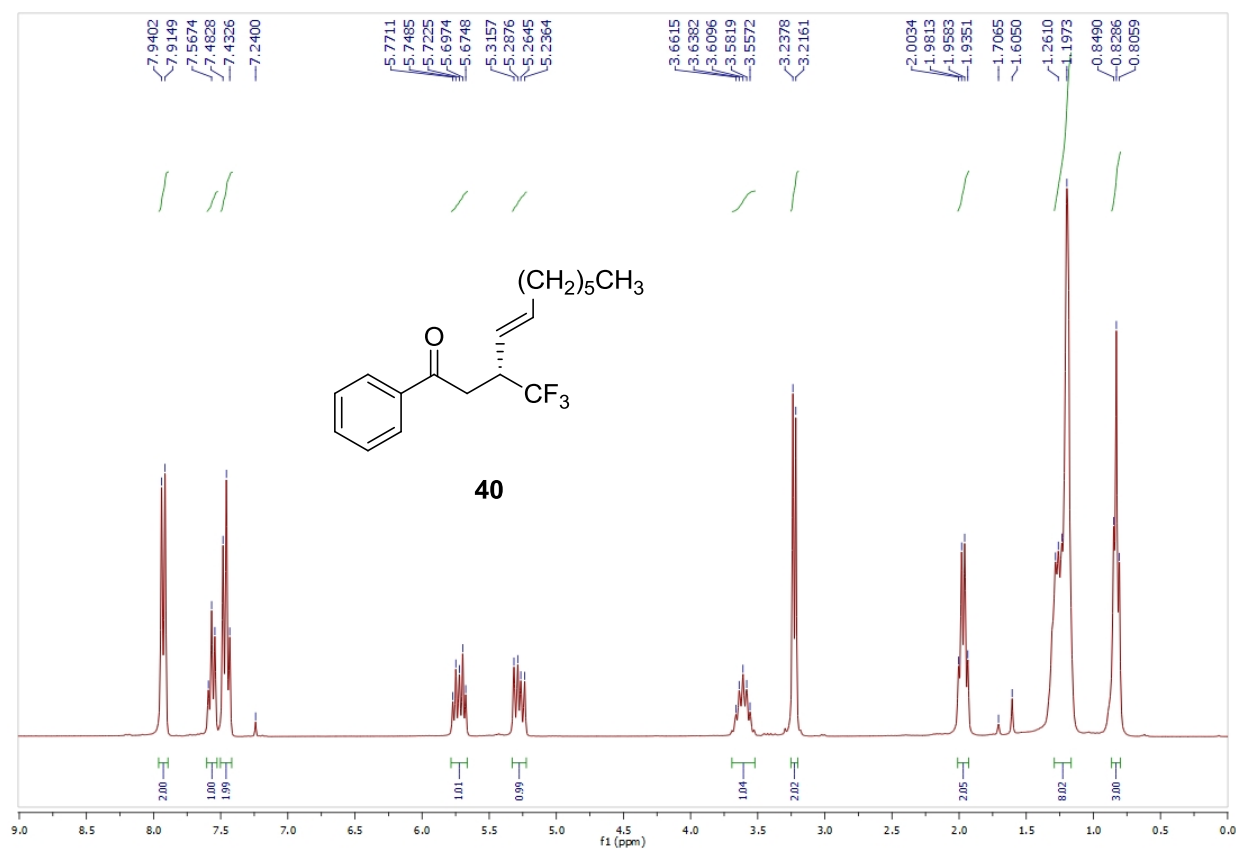
The enantiomeric purity of the product was determined by HPLC on a ChiralCel OD-H column (hexanes/*i*-PrOH = 99.7/0.3, flow rate = 0.5 mL/min),  $t_R = 19.5$  min (*S*),  $t_R = 31.8$  min (*R*).

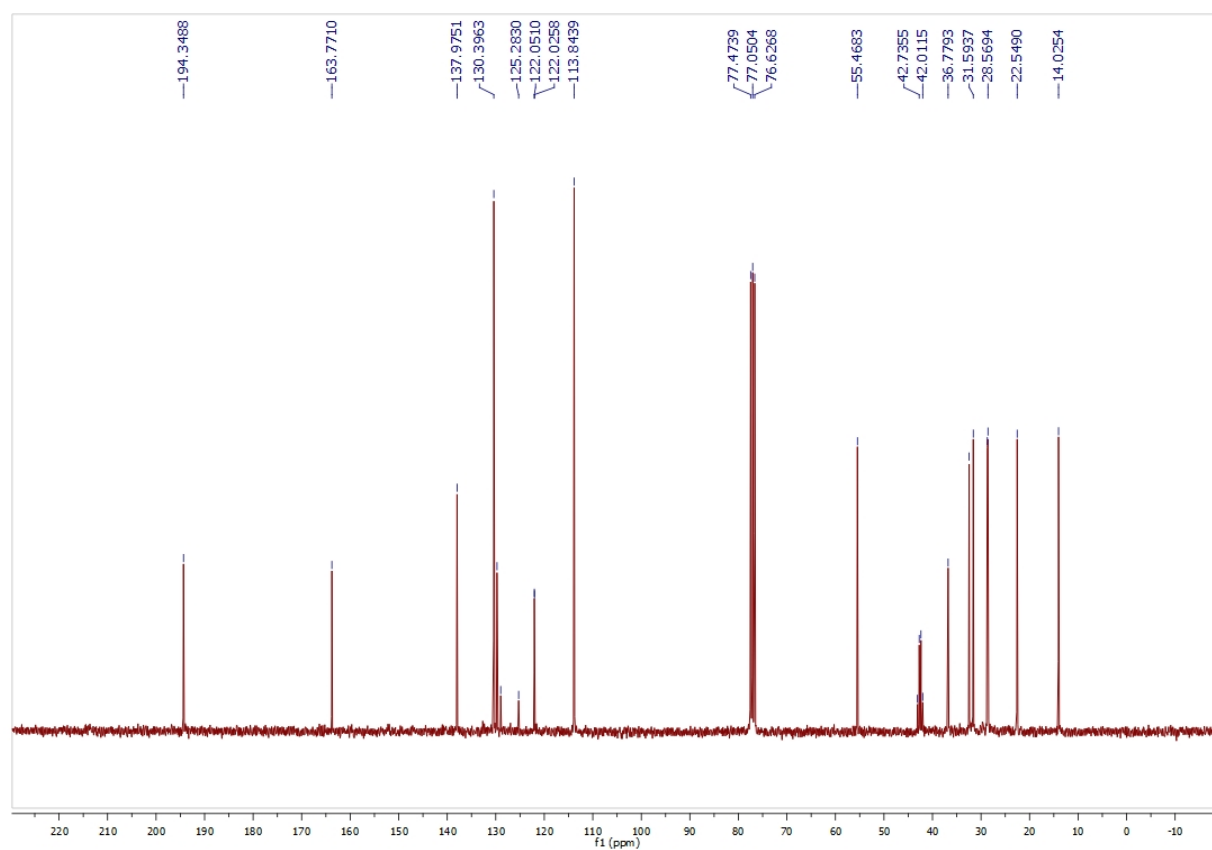
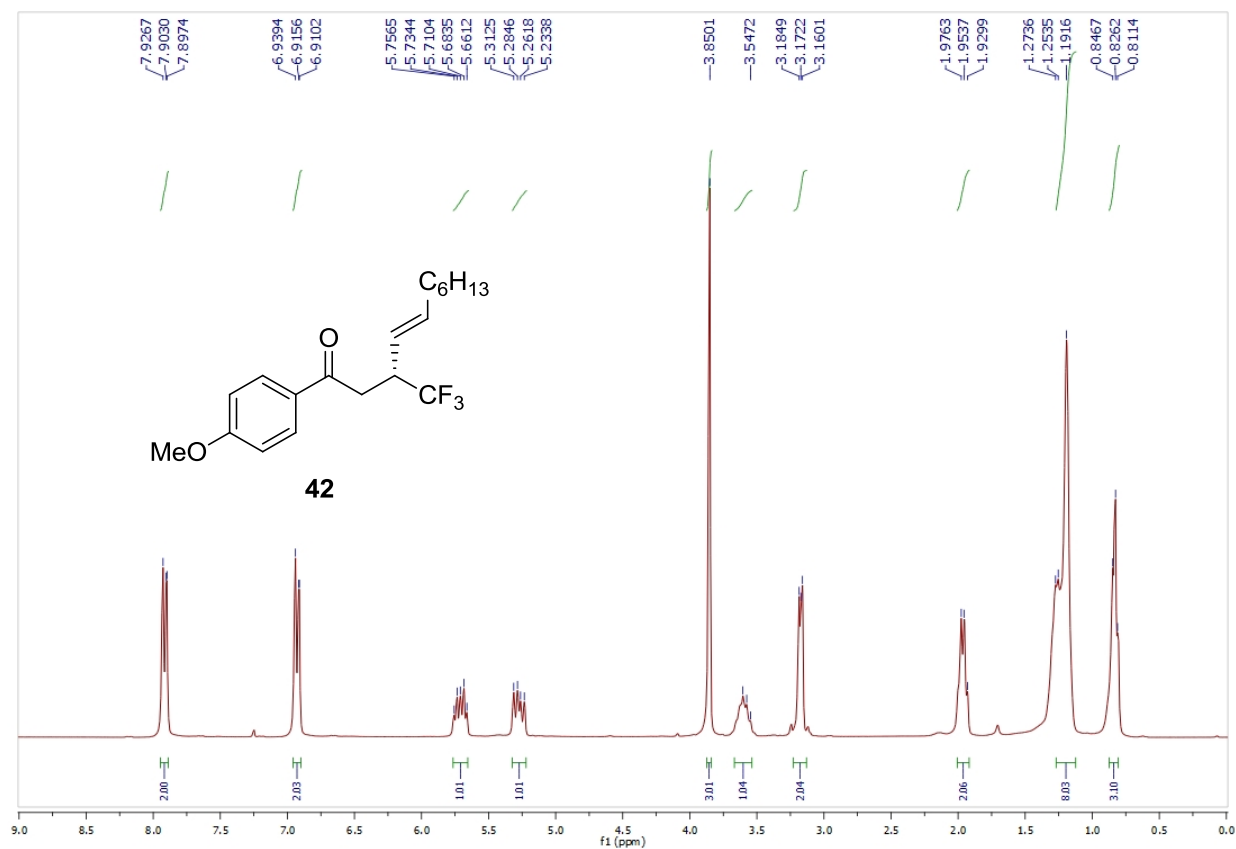
# Appendix

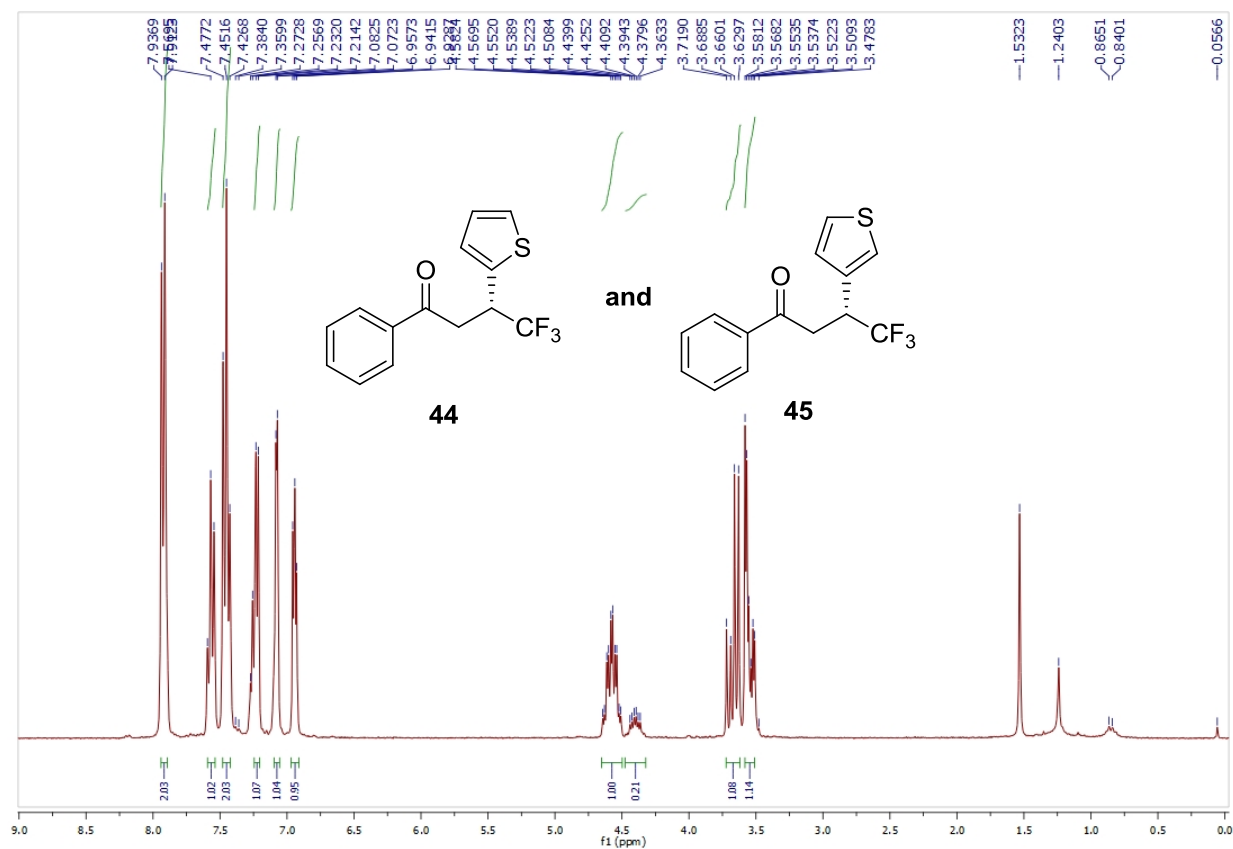


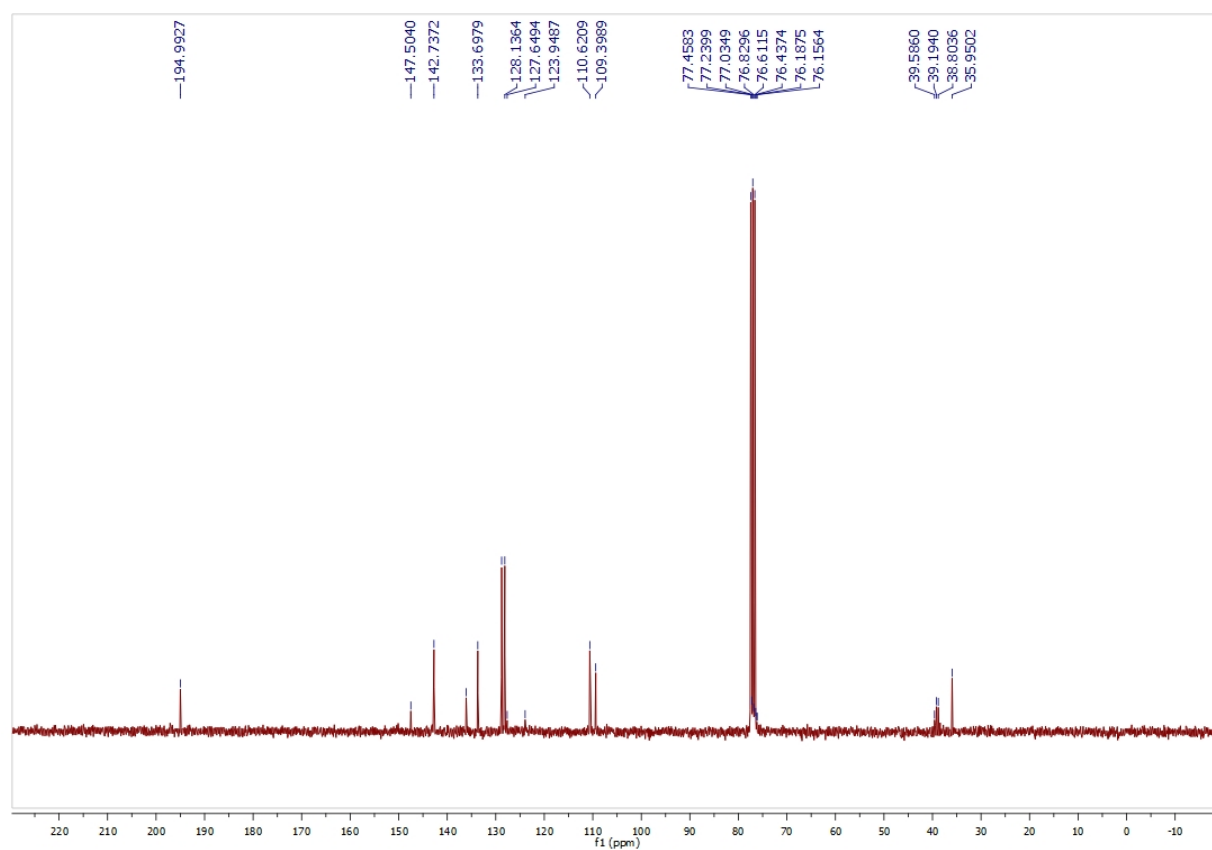
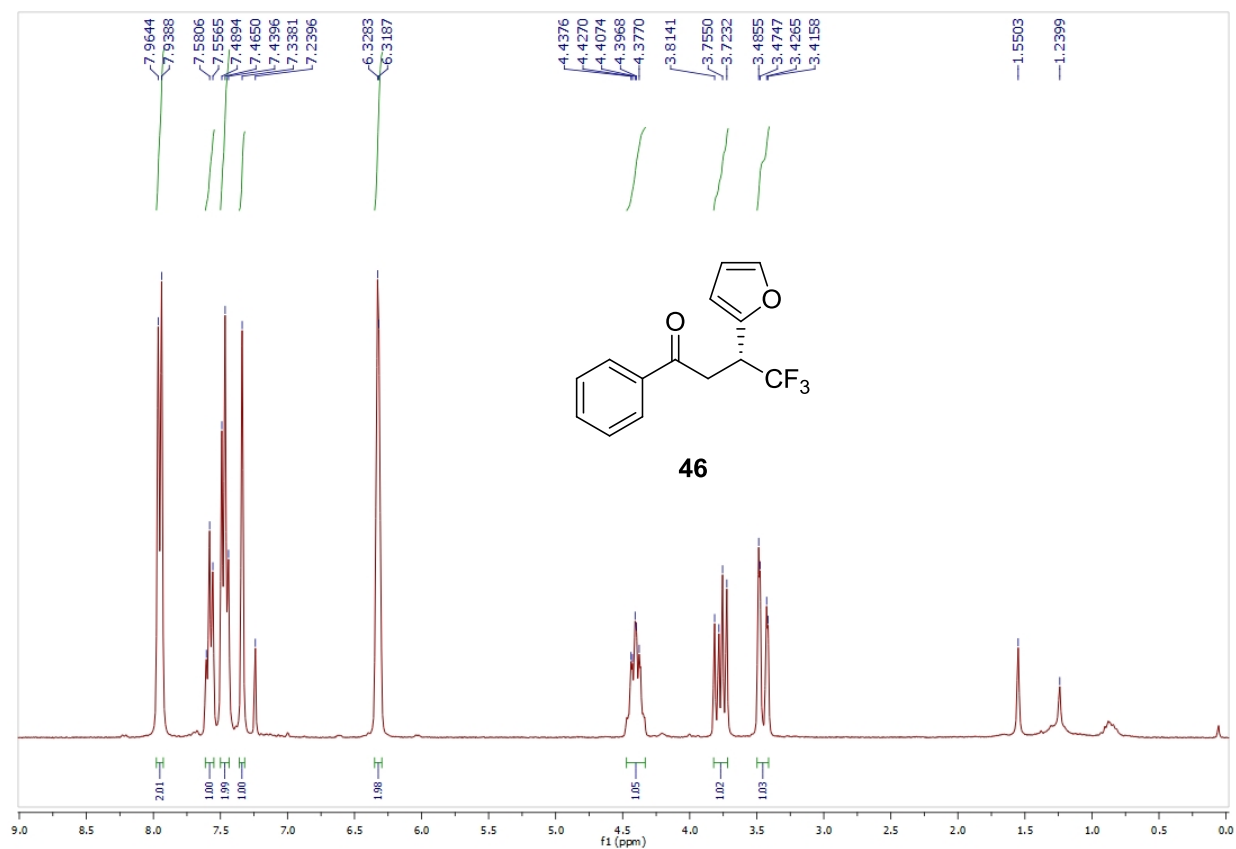












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